1636

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of	:	**PORTNOY, Daniel A.**
Patent No.	:	**6,287,556**
Issued	:	**September 11, 2001**
Title	:	**INTRACELLULAR DELIVERY VEHICLES**
Application Serial No.	:	**09/469,197**
Filed	:	**December 21, 1999**
Examiner	:	**McGarry; Sean**
Art Unit	:	**1636**
For	:	**Ex parte re-examination -6,287,556**

Central Reexamination Unit (CRU)
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Alexandria, VA 22313-1450

RESPONSE TO NOTICE OF FAILURE TO COMPLY WITH EX PARTE REEXAMINATION REQUEST FILING REQUIREMENTS (37 CFR 1.510(C))

Sir:

In response to a Notice of Failure to Comply with Ex Parte Reexamination Request Filing Requirements (37 CFR 1.510(c)), dated October 11, 2007 issued by the United States Patent and Trademark Office in connection with the above-identified Application, Requestor attaches under 37 CFR 1.510(a) and (b), a Replacement Statement pointing out each substantial new question of patentability based on the cited patents and/or printed publications, and a detailed explanation of the pertinency and manner of applying the patents and/or printed publications to every claim for which reexamination is requested. Specifically, Requester attaches a Replacement Statement and Explanation under 37 CFR 1.510(b)(1) and (2) and a Certificate of Service providing that a copy of the Replacement Statement & Explanation has been served in its entirety to the Attorney of Record.

The Replacement Statement and Explanation discusses every patent or printed publication cited on PTO/SB/08 in at least one proposed rejection identifying a substantial new question of patentability and in a corresponding detailed explanation for which request is discussed in at least one proposed rejection statement and in the corresponding explanation.

Requester did not add or delete any patents and/or printed publications as set for on the original filed PTO/SB/08 which were relied upon in the original Statement. Therefore, this Response is in compliance with 37 CFR 1.510 (b) (c)).

If any additional fee is required, the undersigned attorney/agent hereby authorizes the Patent Office to charge such additional fee to Deposit Account 50-3355.

Respectfully submitted,

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Dated: November 7, 2007

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Reexamination of United States Patent No. Patent 6,287,556

CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of November, 2007, a true and correct copy of the following document:

1. Response to Notice of Failure to Comply with Ex Parte Reexamination request filing Requirements (37 CFR 1.510 (c))
2. Replacement Statement and Explanation under 37 CFR.1.510(B)(1)&(2)
3. PTO/SB/08
4. Exhibits A-F

was caused to be served on the attorneys of record at the following address:

Richard Aron Osman,
Science and Technology Law Group,
4070 Calle Isabella, San Clemente, CA 92672

By Federal Express Overnight Delivery

Leah Herzberg

Dated: November 7, 2007

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IN the UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of	**: PORTNOY, Daniel A.**
Patent No.	**: 6,287,556**
Issued	**: September 11, 2001**
Title	**: INTRACELLULAR DELIVERY VEHICLES**
Application Serial No.	**: 09/469,197**
Filed	**: December 21, 1999**
Examiner	**: McGarry; Sean**
Art Unit	**: 1636**
Requester	**: Advaxis, Inc.**

REQUEST FOR *EX PARTE*
REEXAMINATION OF U.S. PATENT NO. 6,287,556
REPLACEMENT STATEMENT & EXPLANATION UNDER 37 CFR 1.510(B)(1) & (2)

I. REPLACEMENT STATEMENT OF SUBSTANTIAL NEW QUESTION OF PATENTABILITY

The following statement is submitted pursuant to 37 C.F.R. §1.510(b) (1). This request for re-examination of US Patent No. 6,287,556 (the "'556 Patent"), entitled Intracellular Delivery Vehicles.

A. Replacement Statement about The '556 Patent

The '556 patent issued on September 11, 2001, from the United States Patent Application No. 09/469,197, filed on December 21, 1999. United States Patent Application Serial No. 09/469,197 was a Continuation Application of United States Patent Application Serial No. 09/133,914, now United States Patent No. 6,004,556, filed on August 13, 1998.

B. References Newly Cited Not Considered by the Examiner

There are substantial new questions of patentability based at least upon the following references:

(A) Gentschev I, Mollenkopf H, Sokolovic Z, Hess J, Kaufmann SH, Goebel W. Development of antigen-delivery systems, based on the Escherichia coli hemolysin secretion pathway. Gene. 1996 Nov 7; 179(1):133-40. T Gentschev I. et al. attached as Exhibit A is prior art to the '556 Patent under 35 U.S.C. § 102(b) because it was published over one year prior to the earliest filing date of the '556 Patent and under 35 U.S.C. §103.

(B) Bielecki J, Youngman P, Connelly P, Portnoy DA. Bacillus subtilis expressing a haemolysin gene from Listeria monocytogenes can grow in mammalian cells. Nature. 1990 May 10; 345(6271):175-6. Bielecki J. et al. attached as Exhibit B is prior art to the '556 Patent under 35 U.S.C. § 102(b) because it was published over one year prior to the earliest filing date of the '556 Patent and under 35 U.S.C. §103.

(C) Hess J, Miko D, Catic A, Lehmensiek V, Russell DG, Kaufmann SH. Mycobacterium bovis Bacille Calmette-Guerin strains secreting listeriolysin of Listeria monocytogenes. Proc Natl Acad Sci U S A. 1998 Apr 28; 95(9):5299-304. Hess J. et al. 1998 attached as Exhibit C is prior art to the '556 Patent under 35 U.S.C. § 102(a) because it was published less than a year prior to the earliest filing date of the '556 Patent and under 35 U.S.C. §103.

(D) Schmidt H, Beutin L, Karch H. Molecular analysis of the plasmid-encoded hemolysin of Escherichia coli O157:H7 strain EDL 933. Infect Immun. 1995 Mar; 63(3):1055-61. Schmidt H. et al. attached as Exhibit D is prior art to the

'556 Patent under 35 U.S.C. § 102(b) because it was published over one year prior to the earliest filing date of the '556 Patent and under 35 U.S.C. §103.

(E) US Patent No. 5,824,538 (the "US'538 Patent"), issued to Branstrom, AA. et al, attached as Exhibit E. The Application that led to the US'538 Patent was filed on September 6, 1995 and the patent issued on October 20, 1998. The US'538 Patent is prior art to the '556 Patent at least under 35 U.S.C. §§ 102(e) and under 35 U.S.C. §103.

(F) Dietrich G, Bubert A, Gentschev I, Sokolovic Z, Simm A, Catic A, Kaufmann SH, Hess J, Szalay AA, Goebel W. Delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide Listeria monocytogenes. Nat Biotechnol. 1998 Feb; 16(2):181-5. Dietrich et al. attached as Exhibit F is prior art to the '556 Patent under 35 U.S.C. § 102(a) because it was published less than a year prior to the earliest filing date of the '556 Patent and under 35 U.S.C. §103.

C. Replacement Statement of Substantial New Question of Patentability

Based at least on the above references, this request presents the following substantial new questions of patentability:

1. A substantial new question of patentability as to claim 1 is raised by the Gentschev reference. Claims 1 of the '556 Patent is unpatentable under 35 U.S.C. 102(b) because the subject matter of claim 1 is anticipated by the Gentschev reference.

2. A substantial new question of patentability as to claim 1 is raised by the Gentschev reference. Claims 1 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 1 is obvious over the Gentschev reference.

3. A substantial new question of patentability as to claim 1 is raised by the Gentschev reference in view of the Hess reference. Claims 1 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 1 is obvious over the Gentschev reference in view of the Hess reference.

4. A substantial new question of patentability as to claim 1 is raised by the Gentschev reference in view of US'538 Patent. Claim 1 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 1 is obvious over the Gentschev reference in view of US'538 Patent.

5. A substantial new question of patentability as to claim 1 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference. Claim 1 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 1 is obvious over the Gentschev reference in view of the Bielecki reference and the Hess reference.

6. A substantial new question of patentability as to claim 1 is raised by the Gentschev reference in view of the Schmidt reference. Claim 1 of the '556 Patent is unpatentable obvious under 35 U.S.C. 103 because the subject matter of claim 1 is obvious over the Gentschev reference in view of the Schmidt.

7. A substantial new question of patentability as to claim 16 is raised by the Gentschev reference. Claims 16 of the '556 Patent is unpatentable under 35 U.S.C. 102(b) because the subject matter of claim 16 is anticipated by the Gentschev reference.

8. A substantial new question of patentability as to claim 16 is raised by the Gentschev reference. Claims 16 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 16 is obvious over the Gentschev reference.

9. A substantial new question of patentability as to claim 16 is raised by the Gentschev reference in view of the Hess reference. Claims 16 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 16 is obvious over the Gentschev reference in view of the Hess reference.

10. A substantial new question of patentability as to claim 16 is raised by the Gentschev reference in view of US'538 Patent. Claim 16 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 16 is obvious over the Gentschev reference in view of US'538 Patent.

11. A substantial new question of patentability as to claim 16 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference. Claim 16 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 16 is obvious over the Gentschev reference in view of the Bielecki reference and the Hess reference.

12. A substantial new question of patentability as to claim 16 is raised by the Gentschev reference in view of the Schmidt reference. Claim 16 of the '556 Patent is unpatentable obvious under 35 U.S.C. 103 because the subject matter of claim 16 is obvious over the Gentschev reference in view of the Schmidt.

13. A substantial new question of patentability as to claim 30 is raised by the Gentschev reference. Claims 30 of the '556 Patent is unpatentable under 35 U.S.C. 102(b) because the subject matter of claim 30 is anticipated by the Gentschev reference.

14. A substantial new question of patentability as to claim 30 is raised by the Gentschev reference. Claims 30 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 30 is obvious over the Gentschev reference.

15. A substantial new question of patentability as to claim 30 is raised by the Gentschev reference in view of the Dietrich reference. Claims 30 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 30 is obvious over the Gentschev reference in view of the Dietrich reference.

16. A substantial new question of patentability as to claim 30 is raised by the Gentschev reference in view of US'538 Patent. Claim 30 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 30 is obvious over the Gentschev reference in view of US'538 Patent.

17. A substantial new question of patentability as to claim 30 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference. Claim 30 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 30 is obvious over the Gentschev reference in view of the Bielecki reference and the Hess reference.

18. A substantial new question of patentability as to claim 30 is raised by the Gentschev reference in view of the Schmidt reference. Claim 30 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 30 is obvious over the Gentschev reference in view of the Schmidt.

19. A substantial new question of patentability as to claims 2 and 17 is raised by the Gentschev reference. Claims 2 and 17 of the '556 Patent are unpatentable under 35 U.S.C.102 (b) because the subject matter of claims 2 and 17 is anticipated, over the Gentschev reference.

20. A substantial new question of patentability as to claims 2 and 17 is raised by the Gentschev reference. Claims 2 and 17 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 2 and 17 is obvious, over the Gentschev reference.

21. A substantial new question of patentability as to claims 2 and 17 is raised by the Gentschev reference in view of the Hess reference. Claims 2 and 17 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 2 and 17 is obvious, over the Gentschev reference in view of the Hess reference.

22. A substantial new question of patentability as to claims 2 and 17 is raised by the Gentschev reference in view of US'538 Patent. Claims 2 and 17 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 2 and 17 is obvious, over the Gentschev reference in view of US'538 Patent.

23. A substantial new question of patentability as to claims 2 and 17 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference. Claims 2 and 17 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 2 and 17 is obvious, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

24. A substantial new question of patentability as to claims 2 and 17 is raised by the Gentschev reference in view of the Schmidt reference. Claims 2 and 17 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 2 and 17 is obvious, over the Gentschev reference in view of the Schmidt reference.

25. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference. Claims 3 and 18 of the '556 Patent are unpatentable under 35 U.S.C.102 (b) because the subject matter of claims 3 and 18 is anticipated, over the Gentschev reference.

26. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference. Claims 3 and 18 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 3 and 18 is obvious, over the Gentschev reference.

27. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference in view of the Hess reference. Claims 3 and 18 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 3 and 18 is obvious, over the Gentschev reference in view of the Hess reference.

28. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference in view of US'538 Patent. Claims 3 and 18 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 3 and 18 is obvious, over the Gentschev reference in view of US'538 Patent.

29. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference. Claims 3 and 18 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 3 and 18 is obvious, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

30. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference in view of the Schmidt reference. Claims 3 and 18 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 3 and 18 is obvious, over the Gentschev reference in view of the Schmidt reference.

31. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference and the Bielecki reference. Claims 3 and 18 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 3 and 18 is obvious, over the Gentschev reference and the Bielecki reference.

32. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference and the Bielecki reference in view of the Hess reference. Claims 3 and 18 of the '556 Patent are unpatentable under 35 U.S.C.103 because

the subject matter of claims 3 and 18 is obvious, over the Gentschev reference and the Bielecki reference in view of the Hess reference.

33. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference and the Bielecki reference in view of US'538 Patent. Claims 3 and 18 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 3 and 18 is obvious, over the Gentschev reference and the Bielecki reference in view of US'538 Patent.

34. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference and the Bielecki reference in view of the Bielecki reference and the Hess reference. Claims 3 and 18 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 3 and 18 is obvious, over the Gentschev reference and the Bielecki reference in view of the Bielecki reference and the Hess reference.

35. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference and the Bielecki reference in view of the Schmidt reference. Claims 3 and 18 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 3 and 18 is obvious, over the Gentschev reference and the Bielecki reference in view of the Schmidt reference.

36. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference and the Dietrich reference. Claims 4 and 19 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 4 and 19 is obvious, over the Gentschev reference and the Dietrich reference.

37. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference. Claims 4 and 19 of the '556 Patent are unpatentable under 35 U.S.C.103 because

the subject matter of claims 4 and 19 is obvious, over the Gentschev reference and the Dietrich reference in view of the Hess reference.

38. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference and the Dietrich reference in view of US'538 Patent. Claims 4 and 19 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 4 and 19 is obvious, over the Gentschev reference and the Dietrich reference in view of US'538 Patent.

39. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference. Claims 4 and 19 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 4 and 19 is obvious, over the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference.

40. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference. Claims 4 and 19 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 4 and 19 is obvious, over the Gentschev reference and the Dietrich reference in view of the Schmidt reference.

41. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference, the Dietrich reference, and the Galan reference. Claims 4 and 19 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 4 and 19 is obvious, over the Gentschev reference, the Dietrich reference, and the Galan reference.

42. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference, the Dietrich reference, and the Galan reference in view of the

Hess reference. Claims 4 and 19 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 4 and 19 is obvious, over the Gentschev reference, the Dietrich reference, and the Galan reference in view of the Hess reference.

43. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference, the Dietrich reference, and the Galan reference in view of US'538 Patent. Claims 4 and 19 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 4 and 19 is obvious, over the Gentschev reference, the Dietrich reference, and the Galan reference in view of US'538 Patent.

44. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference, the Dietrich reference, and the Galan reference in view of the Bielecki reference and the Hess reference. Claims 4 and 19 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 4 and 19 is obvious, over the Gentschev reference, the Dietrich reference, and the Galan reference reference in view of the Bielecki reference and the Hess reference.

45. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference, the Dietrich reference, and the Galan reference in view of the Schmidt reference. Claims 4 and 19 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 4 and 19 is obvious, over the Gentschev reference, the Dietrich reference, and the Galan reference in view of the Schmidt reference.

46. A substantial new question of patentability as to claims 5 and 20 is raised by the Gentschev reference. Claims 5 and 20 of the '556 Patent are unpatentable under 35 U.S.C.102 (b) because the subject matter of claims 5 and 20 is anticipated, over the Gentschev reference.

47. A substantial new question of patentability as to claims 5 and 20 is raised by the Gentschev reference. Claims 5 and 20 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 5 and 20 is obvious, over the Gentschev reference.

48. A substantial new question of patentability as to claims 5 and 20 is raised by the Gentschev reference in view of the Hess reference. Claims 5 and 20 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 5 and 20 is obvious, over the Gentschev reference in view of the Hess reference.

49. A substantial new question of patentability as to claims 5 and 20 is raised by the Gentschev reference in view of US'538 Patent. Claims 5 and 20 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 5 and 20 is obvious, over the Gentschev reference in view of US'538 Patent.

50. A substantial new question of patentability as to claims 5 and 20 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference. Claims 5 and 20 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 5 and 20 is obvious, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

51. A substantial new question of patentability as to claims 5 and 20 is raised by the Gentschev reference in view of the Schmidt reference. Claims 5 and 20 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 5 and 20 is obvious, over the Gentschev reference in view of the Schmidt reference.

52. A substantial new question of patentability as to claims 6, 21, and 32 is raised by the Gentschev reference and the Dietrich reference. Claims 6, 21, and 32 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 6, 21, and 32 is obvious, over the Gentschev and the Dietrich reference.

53. A substantial new question of patentability as to claims 6, 21, and 32 is raised by the Gentschev reference and the Dietrich reference in view of US'538 Patent. Claims 6, 21, and 32 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 6, 21, and 32 is obvious, over the Gentschev and the Dietrich reference in view of US'538 Patent.

54. A substantial new question of patentability as to claims 6, 21, and 32 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference and the Bielecki reference. Claims 6, 21, and 32 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 6, 21, and 32 is obvious, over the Gentschev and the Dietrich reference in view of the Hess reference and the Bielecki reference.

55. A substantial new question of patentability as to claims 6 and 21 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference. Claims 6 and 21 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 6 and 21 is obvious, over the Gentschev and the Dietrich reference in view of the Hess reference.

56. A substantial new question of patentability as to claim 32 is raised by the Gentschev reference and the Dietrich reference in view of the Dietrich reference. Claim 32 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claim 32 is obvious, over the Gentschev and the Dietrich reference in view of the Dietrich reference.

57. A substantial new question of patentability as to claims 6, 21, and 32 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference. Claims 6, 21, and 32 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 6, 21, and 32 is obvious, over the Gentschev and the Dietrich reference in view of the Schmidt reference.

58. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference. Claims 7, 22, and 33 of the '556 Patent are unpatentable under 35 U.S.C.102 (b) because the subject matter of claims 7, 22, and 33 is anticipated, over the Gentschev reference.

59. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference. Claims 7, 22, and 33 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 7, 22, and 33 is obvious, over the Gentschev reference.

60. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference in view of US'538 Patent. Claims 7, 22, and 33 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 7, 22, and 33 is obvious, over the Gentschev reference in view of US'538 Patent.

61. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference in view of the Hess reference and the Bielecki reference. Claims 7, 22, and 33 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 7, 22, and 33 is obvious, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

62. A substantial new question of patentability as to claims 7 and 22 is raised by the Gentschev reference in view of the Hess reference. Claims 7 and 22 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 7 and 22 is obvious, over the Gentschev reference in view of the Hess reference.

63. A substantial new question of patentability as to claim 33 is raised by the Gentschev reference in view of the Dietrich reference. Claim 33 of the '556 Patent

are unpatentable under 35 U.S.C.103 because the subject matter of claim 33 is obvious, over the Gentschev reference in view of the Dietrich reference.

64. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference in view of the Schmidt reference. Claims 7, 22, and 33 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 7, 22, and 33 is obvious, over the Gentschev reference in view of the Schmidt reference.

65. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference and the Schmidt reference. Claims 7, 22, and 33 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 7, 22, and 33 is obvious, over the Gentschev reference and the Schmidt reference.

66. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference and the Schmidt reference in view of US'538 Patent. Claims 7, 22, and 33 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 7, 22, and 33 is obvious, over the Gentschev reference and the Schmidt reference in view of US'538 Patent.

67. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference and the Schmidt reference in view of the Hess reference and the Bielecki reference. Claims 7, 22, and 33 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 7, 22, and 33 is obvious, over the Gentschev reference and the Schmidt reference in view of the Hess reference and the Bielecki reference.

68. A substantial new question of patentability as to claims 7 and 22 is raised by the Gentschev reference and the Schmidt reference in view of the Hess reference.

Claims 7 and 22 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 7 and 22 is obvious, over the Gentschev reference and the Schmidt reference in view of the Hess reference.

69. A substantial new question of patentability as to claim 33 is raised by the Gentschev reference and the Schmidt reference in view of the Dietrich reference. Claim 33 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claim 33 is obvious, over the Gentschev reference and the Schmidt reference in view of the Dietrich reference.

70. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference and the Schmidt reference in view of the Schmidt reference. Claims 7, 22, and 33 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 7, 22, and 33 is obvious, over the Gentschev reference and the Schmidt reference in view of the Schmidt reference.

71. A substantial new question of patentability as to claims 8, 23, and 34 is raised by the Gentschev reference. Claims 8, 23, and 34 of the '556 Patent are unpatentable under 35 U.S.C.102 (b) because the subject matter of claims 8, 23, and 34 is anticipated, over the Gentschev reference.

72. A substantial new question of patentability as to claims 8, 23, and 34 is raised by the Gentschev reference. Claims 8, 23, and 34 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 8, 23, and 34 is obvious, over the Gentschev reference.

73. A substantial new question of patentability as to claims 8, 23, and 34 is raised by the Gentschev reference in view of US'538 Patent. Claims 8, 23, and 34 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of

claims 8, 23, and 34 is obvious, over the Gentschev reference in view of US'538 Patent.

74. A substantial new question of patentability as to claims 8, 23, and 34 is raised by the Gentschev reference in view of the Hess reference and the Bielecki reference. Claims 8, 23, and 34 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 8, 23, and 34 is obvious, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

75. A substantial new question of patentability as to claims 8 and 23 is raised by the Gentschev reference in view of the Hess reference. Claims 8 and 23 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 8 and 23 is obvious, over the Gentschev reference in view of the Hess reference.

76. A substantial new question of patentability as to claim 34 is raised by the Gentschev reference in view of the Dietrich reference. Claim 34 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claim 34 is obvious, over the Gentschev reference in view of the Dietrich reference.

77. A substantial new question of patentability as to claims 8, 23, and 34 is raised by the Gentschev reference in view of the Schmidt reference. Claims 8, 23, and 34 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 8, 23, and 34 is obvious, over the Gentschev reference in view of the Schmidt reference.

78. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference. Claims 9 and 35 of the '556 Patent are unpatentable under 35 U.S.C.102 (b) because the subject matter of claims 9 and 35 is anticipated, over the Gentschev reference.

79. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference. Claims 9 and 35 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 9 and 35 is obvious, over the Gentschev reference.

80. A substantial new question of patentability as to claim 9 is raised by the Gentschev reference in view of the Hess reference. Claim 9 of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claim 9 is obvious, over the Gentschev reference in view of the Hess reference.

81. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference in view of US'538 Patent. Claims 9 and 35 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of 9 and 35 is obvious, over the Gentschev reference in view of US'538 Patent.

82. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference. Claims 9 and 35 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 9 and 35 is obvious, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

83. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference in view of the Schmidt reference. Claims 9 and 35 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 9 and 35 is obvious, over the Gentschev reference in view of the Schmidt reference.

84. A substantial new question of patentability as to claim 35 is raised by the Gentschev reference in view of the Dietrich reference. Claim 35 of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claims 35 is obvious, over the Gentschev reference in view of the Dietrich reference.

85. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference and the Dietrich reference. Claims 5 and 20 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 5 and 20 is obvious, over the Gentschev reference and the Dietrich reference.

86. A substantial new question of patentability as to claim 9 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference. Claim 9 of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claim 9 is obvious, over the Gentschev reference and the Dietrich reference in view of the Hess reference.

87. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference and the Dietrich reference in view of US'538 Patent. Claims 9 and 35 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of 9 and 35 is obvious, over the Gentschev reference and the Dietrich reference in view of US'538 Patent.

88. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference. Claims 9 and 35 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 9 and 35 is obvious, over the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference.

89. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference. Claims 9 and 35 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 9 and 35 is obvious, over the Gentschev reference and the Dietrich reference in view of the Schmidt reference.

90. A substantial new question of patentability as to claim 35 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference. Claim 35 of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claims 35 is obvious, over the Gentschev reference and the Dietrich reference in view of the Dietrich reference.

91. A substantial new question of patentability as to claims 10, 24, and 36 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference. Claims 10, 24, and 36 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 10, 24, and 36 is obvious, over self admitted Prior Art and the Gentschev reference.

92. A substantial new question of patentability as to claims 10, 24, and 36 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of US'538 Patent. Claims 10, 24, and 36 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 10, 24, and 36 is obvious, over self admitted Prior Art and the Gentschev reference in view of US'538 Patent.

93. A substantial new question of patentability as to claims 10, 24, and 36 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Hess reference and the Bielecki reference. Claims 10, 24, and 36 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 10, 24, and 36 is obvious, over self admitted Prior Art and the Gentschev reference in view the Hess reference and the Bielecki reference.

94. A substantial new question of patentability as to claims 10 and 24 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Hess reference. Claims 10 and 24 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 10 and 24 is obvious, over self admitted Prior Art and the Gentschev reference in view the Hess reference.

95. A substantial new question of patentability as to claim 36 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Dietrich reference. Claim 36of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claim 36 is obvious, over self admitted Prior Art and the Gentschev reference in view the Dietrich reference.

96. A substantial new question of patentability as to claims 10, 24, and 36 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Schmidt reference. Claims 10, 24, and 36 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 10, 24, and 36 is obvious, over self admitted Prior Art and the Gentschev reference in view the Schmidt reference.

97. A substantial new question of patentability as to claims 11, 25, and 37 is raised by the Gentschev reference and the Dietrich reference. Claims 11, 25, and 37 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 11, 25, and 37 is obvious, over the Gentschev reference and the Dietrich reference.

98. A substantial new question of patentability as to claims 11, 25, and 37 is raised by the Gentschev reference and the Dietrich reference in view of US'538 Patent. Claims 11, 25, and 37 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 11, 25, and 37 is obvious, over the Gentschev reference and the Dietrich reference in view of US'538 Patent.

99. A substantial new question of patentability as to claims 11, 25, and 37 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference and the Bielecki reference. Claims 11, 25, and 37 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 11, 25, and

37 is obvious, over the Gentschev reference and the Dietrich reference in view of the Hess reference and the Bielecki reference.

100. A substantial new question of patentability as to claims 11 and 25 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference. Claims 11 and 25 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 11 and 25 is obvious, over the Gentschev reference and the Dietrich reference in view of the Hess reference.

101. A substantial new question of patentability as to claim 37 is raised by the Gentschev reference and the Dietrich reference in view of the Dietrich reference. Claim 37 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claim 37 is obvious, over the Gentschev reference and the Dietrich reference in view of the Dietrich reference.

102. A substantial new question of patentability as to claims 11, 25, and 37 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference. Claims 11, 25, and 37 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 11, 25, and 37 is obvious, over the Gentschev reference and the Dietrich reference in view of the Schmidt reference.

103. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference. 12, 26, and 38 of the '556 Patent are unpatentable under 35 U.S.C.102 (b) because the subject matter of claims 12, 26, and 38 is anticipated, over the Gentschev reference.

104. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference. 12, 26, and 38 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 12, 26, and 38 is obvious, over the Gentschev reference.

105. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference in view of US'538 Patent. Claims 12, 26, and 38 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 12, 26, and 38 is obvious, over the Gentschev reference in view of US'538 Patent.

106. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference in view of the Hess reference and the Bielecki reference. Claims 12, 26, and 38 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 12, 26, and 38 is obvious, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

107. A substantial new question of patentability as to claims 121 and 26 is raised by the Gentschev reference in view of the Hess reference. Claims 12 and 26 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 12 and 265 is obvious, over the Gentschev reference in view of the Hess reference.

108. A substantial new question of patentability as to claim 38 is raised by the Gentschev reference in view of the Dietrich reference. Claim 38 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claim 38 is obvious, over the Gentschev reference in view of the Dietrich reference.

109. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference in view of the Schmidt reference. Claims 12, 26, and 38 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 12, 26, and 38 is obvious, over the Gentschev reference in view of the Schmidt reference.

110. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference and the Schmidt reference. Claims 12, 26, and 38 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 12, 26, and 38 is obvious, over the Gentschev reference and the Schmidt reference.

111. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference and the Schmidt reference in view of US'538 Patent. Claims 12, 26, and 38 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 12, 26, and 38 is obvious, over the Gentschev reference and the Schmidt reference in view of US'538 Patent.

112. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference and the Schmidt reference in view of the Hess reference and the Bielecki reference. Claims 12, 26, and 38 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 12, 26, and 38 is obvious, over the Gentschev reference and the Schmidt reference in view of the Hess reference and the Bielecki reference.

113. A substantial new question of patentability as to claims 12 and 26 is raised by the Gentschev reference and the Schmidt reference in view of the Hess reference. Claims 12 and 26 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 12 and 26 is obvious, over the Gentschev reference and the Schmidt reference in view of the Hess reference.

114. A substantial new question of patentability as to claim 38 is raised by the Gentschev reference and the Schmidt reference in view of the Dietrich reference. Claim 38 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claim 38 is obvious, over the Gentschev reference and the Schmidt reference in view of the Dietrich reference.

115. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference and the Schmidt reference in view of the Schmidt reference. Claims 12, 26, and 38 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 12, 26, and 38 is obvious, over the Gentschev reference and the Schmidt reference in view of the Schmidt reference.

116. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich reference. Claims 13, 27, and 39 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 12, 26, and 38 is obvious, over the Gentschev reference and the Dietrich reference.

117. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich reference in view of US'538 Patent. Claims 13, 27, and 39 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 13, 27, and 39 is obvious, over the Gentschev reference and the Dietrich reference in view of US'538 Patent.

118. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference and the Bielecki reference. Claims 13, 27, and 39 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 13, 27, and 39 is obvious, over the Gentschev reference and the Dietrich reference in view of the Hess reference and the Bielecki reference.

119. A substantial new question of patentability as to claims 13 and 27 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference. Claims 13 and 27 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 13 and 27 is obvious, over the Gentschev reference and the Dietrich t reference in view of the Hess reference.

120. A substantial new question of patentability as to claim 39 is raised by the Gentschev reference and the Dietrich reference in view of the Dietrich reference. Claim 39 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claim 39 is obvious, over the Gentschev reference and the Dietrich reference in view of the Dietrich reference.

121. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich t reference in view of the Schmidt reference. Claims 13, 27, and 39 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 13, 27, and 39 is obvious, over the Gentschev reference and the Dietrich reference in view of the Schmidt reference.

122. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference and the Dietrich reference. Claims 14, 28, and 40 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 14, 28, and 40 is obvious, over the Gentschev reference and the Dietrich reference.

123. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference and the Dietrich reference in view of US'538 Patent. Claims 14, 28, and 40 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 14, 28, and 40 is obvious, over the Gentschev reference and the Dietrich reference in view of US'538 Patent.

124. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference and the Bielecki reference. Claims 14, 28, and 40 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 14, 28, and 40 is obvious, over the Gentschev reference and the Dietrich reference in view of the Hess reference and the Bielecki reference.

125. A substantial new question of patentability as to claims 14 and 287 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference. Claims 14 and 28 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 14 and 28 is obvious, over the Gentschev reference and the Dietrich t reference in view of the Hess reference.

126. A substantial new question of patentability as to claim 40 is raised by the Gentschev reference and the Dietrich reference in view of the Dietrich reference. Claim 40 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claim 40 is obvious, over the Gentschev reference and the Dietrich reference in view of the Dietrich reference.

127. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference and the Dietrich t reference in view of the Schmidt reference. Claims 14, 28, and 40 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 14, 28, and 40 is obvious, over the Gentschev reference and the Dietrich reference in view of the Schmidt reference.

128. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference. Claims 14, 28, and 40 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 14, 28, and 40 is obvious, over the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference.

129. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of US'538 Patent. Claims 14, 28, and 40 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims

14, 28, and 40 is obvious, over the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of US'538 Patent.

130. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the Hess reference and the Bielecki reference. Claims 14, 28, and 40 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 14, 28, and 40 is obvious, over the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the Hess reference and the Bielecki reference.

131. A substantial new question of patentability as to claims 14 and 287 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference. Claims 14 and 28 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 14 and 28 is obvious, over the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the Hess reference.

132. A substantial new question of patentability as to claim 40 is raised by the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the Dietrich reference. Claim 40 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claim 40 is obvious, over the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the Dietrich reference.

133. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the Schmidt reference. Claims 14, 28, and 40 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 14, 28, and 40 is obvious, over the Gentschev reference, the Dietrich

reference, the Bielecki reference, and the Schmidt reference in view of the Schmidt reference.

134. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference. Claims 15 and 41 of the '556 Patent are unpatentable under 35 U.S.C.102 (b) because the subject matter of claims 15 and 41 is anticipated, over the Gentschev reference.

135. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference. Claims 15 and 41 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 15 and 41 is obvious, over the Gentschev reference.

136. A substantial new question of patentability as to claim 15 is raised by the Gentschev reference in view of the Hess reference. Claim 15 of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claim 15 is obvious, over the Gentschev reference in view of the Hess reference.

137. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference in view of US'538 Patent. Claims 15 and 41 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of 15 and 41 is obvious, over the Gentschev reference in view of US'538 Patent.

138. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference. Claims 15 and 41 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 15 and 41 is obvious, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

139. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference in view of the Schmidt reference. Claims 15 and 41 of the

'556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 15 and 41 is obvious, over the Gentschev reference in view of the Schmidt reference.

140. A substantial new question of patentability as to claim 41 is raised by the Gentschev reference in view of the Dietrich reference. Claim 41 of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claims 41 is obvious, over the Gentschev reference in view of the Dietrich reference.

141. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference and the Dietrich reference. Claims 15 and 41 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 15 and 41 is obvious, over the Gentschev reference and the Dietrich reference.

142. A substantial new question of patentability as to claim 15 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference. Claim 15 of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claim 15 is obvious, over the Gentschev reference and the Dietrich reference in view of the Hess reference.

143. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference and the Dietrich reference in view of US'538 Patent. Claims 15 and 41 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of 15 and 41 is obvious, over the Gentschev reference and the Dietrich reference in view of US'538 Patent.

144. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference. Claims 15 and 41 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 15 and 41 is

obvious, over the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference.

145. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference. Claims 15 and 41 of the '556 Patent are unpatentable under 35 U.S.C.103 because the subject matter of claims 15 and 41 is obvious, over the Gentschev reference and the Dietrich reference in view of the Schmidt reference.

146. A substantial new question of patentability as to claim 41 is raised by the Gentschev reference and the Dietrich reference in view of the Dietrich reference. Claim 41 of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claims 41 is obvious, over the Gentschev reference and the Dietrich reference in view of the Dietrich reference.

147. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference. Claims 29 of the '556 Patent is unpatentable under 35 U.S.C. 102(b) because the subject matter of claim 29 is anticipated by the Gentschev reference.

148. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference. Claims 29 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 29 is obvious over the Gentschev reference.

149. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference in view of the Hess reference. Claims 29 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 29 is obvious over the Gentschev reference in view of the Hess reference.

150. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference in view of US'538 Patent. Claim 29 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 29 is obvious over the Gentschev reference in view of US'538 Patent.

151. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference. Claim 29 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 29 is obvious over the Gentschev reference in view of the Bielecki reference and the Hess reference.

152. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference in view of the Schmidt reference. Claim 29 of the '556 Patent is unpatentable obvious under 35 U.S.C. 103 because the subject matter of claim 29 is obvious over the Gentschev reference in view of the Schmidt.

153. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference and the Hess reference. Claims 29 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 29 is obvious over the Gentschev reference and the Hess reference.

154. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference and the Hess reference in view of the Hess reference. Claims 29 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 29 is obvious over the Gentschev reference and the Hess reference in view of the Hess reference.

155. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference and the Hess reference in view of US'538 Patent. Claim 29 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of

claim 29 is obvious over the Gentschev reference and the Hess reference in view of US'538 Patent.

156. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference and the Hess reference in view of the Bielecki reference and the Hess reference. Claim 29 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 29 is obvious over the Gentschev reference and the Hess reference in view of the Bielecki reference and the Hess reference.

157. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference and the Hess reference in view of the Schmidt reference. Claim 29 of the '556 Patent is unpatentable obvious under 35 U.S.C. 103 because the subject matter of claim 29 is obvious over the Gentschev reference and the Hess reference in view of the Schmidt.

158. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Dietrich reference. Claims 31 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 31 is obvious over the Gentschev reference, US' 538 Patent, and the Dietrich reference.

159. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Dietrich reference. Claims 31 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 31 is obvious over the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Dietrich reference.

160. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of US'538 Patent. Claim 31 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 31 is obvious over the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of US'538 Patent.

161. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Bielecki reference and the Hess reference. Claim 31 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 31 is obvious over the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Bielecki reference and the Hess reference.

162. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Schmidt reference. Claim 31 of the '556 Patent is unpatentable obvious under 35 U.S.C. 103 because the subject matter of claim 31 is obvious over the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Schmidt.

163. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Hess reference. Claims 31 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 31 is obvious over the Gentschev reference, US' 538 Patent, and the Hess reference.

164. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Hess reference in view of the Dietrich reference. Claims 31 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 31 is obvious over the Gentschev reference, US' 538 Patent, and the Hess reference in view of the Dietrich reference.

165. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Hess reference in view of US'538 Patent. Claim 31 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 31 is obvious over the Gentschev reference, US' 538 Patent, and the Hess reference in view of US'538 Patent.

166. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Hess reference in view of the Bielecki reference and the Hess reference. Claim 31 of the '556 Patent is unpatentable under 35 U.S.C. 103 because the subject matter of claim 31 is obvious over the Gentschev reference, US' 538 Patent, and the Hess reference in view of the Bielecki reference and the Hess reference.

167. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Hess reference in view of the Schmidt reference. Claim 31 of the '556 Patent is unpatentable obvious under 35 U.S.C. 103 because the subject matter of claim 31 is obvious over the Gentschev reference, US' 538 Patent, and the Hess reference in view of the Schmidt.

168. A substantial new question of patentability as to claim 42 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference. Claim 42 of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claim 42 is obvious, over self admitted Prior Art and the Gentschev reference.

169. A substantial new question of patentability as to claim 42 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Dietrich reference. Claim 42 of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claim 42 is obvious, over self admitted Prior Art and the Gentschev reference in view of the Dietrich reference.

170. A substantial new question of patentability as to claim 42 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of US'538 Patent. Claim 42 of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claim 42 is obvious, over self admitted Prior Art and the Gentschev reference in view of US'538 Patent.

171. A substantial new question of patentability as to claim 42 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Bielecki reference and the Hess reference. Claim 42 of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claim 42 is obvious, over self admitted Prior Art and the Gentschev reference in view of the Bielecki reference and the Hess reference.

172. A substantial new question of patentability as to claim 42 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Schmidt reference. Claim 42 of the '556 Patent is unpatentable under 35 U.S.C.103 because the subject matter of claim 42 is obvious, over self admitted Prior Art and the Gentschev in view of the Schmidt reference.

The above reference(s) present new subject matter not considered by the Examiner in granting the '556 Patent. For this reason, and based upon the analysis presented below, there is a substantial new question of patentability of claims 1-33 of the '556 Patent. Accordingly, Advaxis, Inc. ("Advaxis" or "Requester"), through its undersigned counsel, respectfully requests reexamination of claims 1-33 of the '556 Patent.

II. PROSECUTION HISTORY OF the '556 PATENT

The '556 Patent original claims 11-65 as filed recited:

> 11. A vaccine comprising a nonvirulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous

promoter which expresses the cytolysin in the bacterium, and a second gene encoding a different foreign antigenic agent.

12. The vaccine of claim 11, wherein the cytolysin is absent a functional signal sequence.

13. The vaccine of claim 11, wherein the cytolysin is listeriolysin.

14. The vaccine of claim 11, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin.

15. The vaccine of claim 11, wherein the bacterium is a laboratory strain of E. coli.

16. The vaccine of claim 11, wherein the bacterium is dead or non-viable.

17. The vaccine of claim 11, wherein the bacterium comprises the cytolysin.

18. The vaccine of claim 11, wherein the agent is synthesized by the bacterium.

19. The vaccine of claim 11, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins.

20. The vaccine of claim 11, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome.

21. The vaccine of claim 11, wherein the bacterium is a dead or nonviable laboratory strain of E. coli.

22. The vaccine of claim 11, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin.

23. The vaccine of claim 11, wherein the bacterium is a dead or nonviable laboratory strain of E. coli and the bacterium comprises the cytolysin.

24. The vaccine of claim 11, wherein the bacterium is a dead or nonviable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin.

25. The vaccine of claim 11, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins.

26. A pharmaceutical composition comprising a nonvirulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding a different foreign therapeutic agent.

27. The composition of claim 26, wherein the cytolysin is absent a functional signal sequence.

28. The composition of claim 26, wherein the cytolysin is listeriolysin.

29. The composition of claim 26, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin.

30. The composition of claim 26, wherein the bacterium is a laboratory strain of E. coli.

31. The composition of claim 26, wherein the bacterium is dead or non-viable.

32. The composition of claim 26, wherein the bacterium comprises the cytolysin.

33. The composition of claim 26, wherein the agent is synthesized by the bacterium.

34. The composition of claim 26, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome.

35. The composition of claim 26, wherein the bacterium is a dead or nonviable laboratory strain of E. coli.

36. The composition of claim 26, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin.

37. The composition of claim 26, wherein the bacterium is a dead or nonviable laboratory strain of E. coli and the bacterium comprises the cytolysin.

38. The composition of claim 26, wherein the bacterium is a dead or nonviable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin.

39. The composition of claim 26, wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor.

40. A method of introducing a foreign antigenic agent into a eukaryotic cell comprising the step of contacting the cell with a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign

functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding the foreign antigenic agent under conditions whereby the agent enters the cell.

41. The method of claim 40, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell.

42. The method of claim 40, wherein the bacterium is dead or non-viable.

43. The method of claim 40, wherein the bacterium comprises the cytolysin.

44. The method of claim 40, wherein the agent is synthesized by the bacterium.

45. The method of claim 40, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins.

46. The method of claim 40, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome.

47. The method of claim 40, wherein the bacterium is a dead or nonviable laboratory strain of E. coli.

48. The method of claim 40, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin.

49. The method of claim 40, wherein the bacterium is a dead or nonviable laboratory strain of E. coli and the bacterium comprises the cytolysin.

50. The method of claim 40, wherein the bacterium is a dead or nonviable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin.

51. The method of claim 40, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins.

52. The method of claim 40, wherein there is no growth or metabolism of the bacterium in the eukaryotic cell.

53. A method of treating a disease comprising the step of introducing a foreign therapeutic agent into a eukaryotic cell comprising the step of contacting the cell with the bacterium of claim 1, under conditions whereby the agent enters the cell.

54. The method of claim 53, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium undergoes lysis and the cytolysin mediates transfer of the therapeutic agent from the vacuole to the cytosol of the cell.

55. The method of claim 53, wherein the bacterium is dead or non-viable.

56. The method of claim 53, wherein the bacterium comprises the cytolysin.

57. The method of claim 53, wherein the agent is synthesized by the bacterium.

58. The method of claim 53, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome.

59. The method of claim 53, wherein the bacterium is a dead or nonviable laboratory strain of E. coli.

60. The method of claim 53, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin.

61. The method of claim 53, wherein the bacterium is a dead or nonviable laboratory strain of E. coli and the bacterium comprises the cytolysin.

62. The method of claim 53, wherein the bacterium is a dead or nonviable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin.

63. The method of claim 53, wherein there is no growth or metabolism of the bacterium in the eukaryotic cell.

64. The method of claim 53, wherein the therapeutic agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor.

65. The method of claim 53, wherein the disease is selected from cancer, infection, degenerative disease, and diabetes.

In an Office Action dated November 21, 2000, the Examiner rejected claims 11, 17, 26, 40-43 under 35 U.S.C. 102(a), as anticipated by Dietrich. Further, the Examiner rejected claims 40-65 under 35 U.S.C. 112, second paragraph, for not containing a method step that relates back to the goal set forth by the preamble. Further, the Examiner rejected claims 53-65 under 35 U.S.C. 112, second paragraph, for having excessive scope in view of the disclosed embodiments.

In a Response dated February 20, 2000, Applicants amended claims 40 and 53 by omitting the phrases "generating an immune response comprising the step of" and "treating a disease comprising the step of," respectively, in the preambles thereof, and canceled claim 65. Applicants traversed the 35 U.S.C. 102 rejections by arguing that "avirulent" was distinct from "attenuated for virulence" in Dietrich (we note that "non-virulent," not "avirulent," was recited in the claims). As evidence for their contention, Applicants cited Higgins et al. which allegedly distinguished between the terms "avirulent" and "attenuated for virulence."

Further, Applicants argued that the "cytolysin" recited in the claims was distinct from the "endolysin" of Dietrich, in that a cytolysin lyses a cell membrane, while an endolysin lyses a bacterial cell wall. As evidence for their contention, Applicants cited Higgins et al, which allegedly distinguished between the two terms.

Further, Applicants argued that the amended claims were enabled and thus allowable under 35 U.S.C. 112.

On April 9, 2001, the Examiner issued a Restriction Requirement, requiring Applicants to elect either Group I (claims 11-52) or Group II (claims 53-64). The Examiner concurrently issued an Examiner's Amendment, canceling claims 43-64 (Applicants had orally agreed to elect Group I), and amending claim 40 to be in independent format. Further, the Examiner issued a Notice of Allowability, indicating that claims 1-52 were allowable in view of the Terminal Disclaimer that had been filed on October 31, 2000, with respect to the '556 Patent, and because "the art search and of record does not teach or fairly suggest the vaccine compositions or methods claimed."

III. SUMMARY OF NEWLY CITED PRIOR ART

It will be recognized that the substance of the prior art is found in Gentschev, Dietrich, US'538 Patent, Bielecki, Hess, Dietrich and the Schmidt reference, and therefore, the '556 Patent is not patentable as being anticipated by the Gentschev reference and/or rendered

obvious in view of the Gentschev reference, either alone and/or in combination with US'538 Patent, Bielecki, and/or Hess, as evidenced by the Schmidt reference.

Gentschev discloses attenuated bacteria expressing the cytolysin LLO:

> "The attenuated Salmonella strains producing these proteins were tested for their potential of inducing protective immunity against L. monocytogenes infection... All mice vaccinated with S. typhimurium SL7207 secreting listeriolysin... survived subsequent L. monocytogenes infection whereas all mice vaccinated with the control strain died" (first paragraph, section 2.4, page 137).
>
> "We have recently shown that a slyA mutation (Libby et al., 1994) also leads to an efficient attenuation of Salmonella. A mutation in this regulatory protein (Ludwig et al., 1995) drastically reduces virulence of S. typhimurium in mice. slyA mutant bacteria are still taken up by the M cells of the Peyer's patches with an efficiency comparable to that of wild-type organisms (J. Daniels, unpublished results) where they persist for a longer time than aroA mutants without destroying the M cells" (page 135, first full paragraph; emphasis added).

Indeed, the Gentschev reference recognizes that the mutated strain can be used for vaccination and the mutation "drastically reduces virulence". Thus, "drastically reduces virulence" and "non-virulent" are one and the same as evidenced in mice in disclosed by Gentschev.

Additionally, Gentschev discloses a nonsecreted foreign functional cytolysin:

> "The construction of the attenuated S. typhimurium aroA strain SL7207 secreting hybrid listeriolysin was achieved by cloning the hly gene of L. monocytogenes EGD into the above described vector plasmid pMOhlyl" (first paragraph, section 2.3, page 136).

> "All mice vaccinated with S. typhimurium SL7207 secreting listeriolysin...fusion protein survived subsequent L. monocytogenes infection whereas all mice vaccinated with the control strain died. Interestingly this protection was not observed when attenuated Salmonella strains were used as live vaccines which synthesized these fusion proteins but did not secrete them. As mentioned above, listeriolysin with the HlyAs C terminus retains cytolytic activity" (first paragraph, section 2.4, page 137; emphasis added). [thus, non-secreted, functional cytolysins were utilized].

Typhimurium aroA strain SL7207 transfected with vector plasmid pMOhlyl comprising hly gene of L. monocytogenes EGD thus, SL7207 strain foreign is transfected with a foreign gene.

Hly encodes LLO, a cytolysin (Abbreviations section on page 133).

Indeed, the Gentschev reference discloses a bacterium comprising a gene encoding a nonsecreted foreign functional cytolysin. This strain was not effective in the mice immunization assay.

Additionally, Gentschev discloses secreted foreign functional cytolysin expressed from several different non-Salmonella promoters, phlyI and plac:

> "All genes (including the hlyAS-fused hybrid gene) are transcribed from the original cis-acting expression sites in front of hlyC and the plasmid pIG carrying the C-terminal part of hlyA (encoding the secretion signal) for the in-frame insertion of heterologous proteins or antigens. In the latter plasmid, the expression of the fused gene is under the control of Plac)..." (first paragraph, section 2.2, page 135).

HlyC is the phlyI promoter, which is found on an E. coli plasmid. Indeed, the Gentschev reference recognizes that the expressed gene is operably linked to a heterologous promoter.

Additionally, Gentschev discloses that the cytolysin is expressed in the bacterium:

> "Interestingly this protection was not observed when attenuated Salmonella strains were used as live vaccines which synthesized these fusion proteins but did not secrete them" (first paragraph, section 2.2, page 135, emphasis added).

Indeed, the Gentschev reference recognizes that cytolysin is expressed in the bacterium.

Finally, Gentschev discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD:

> "Two plasmid systems have been constructed which allow secretion of heterologous proteins via the secretion apparatus of E. coli hemolysin…. The plasmid pMOhlyl contains the intact structural genes hlyC, hlyB and hlyD and two short residual sequences of the hlyA gene…. The construction of the attenuated S. typhimurium aroA strain SL7207 secreting hybrid listeriolysin was achieved by cloning the hly gene of L. monocytogenes EGD into the above described vector plasmid pMOhlyl" (first paragraphs of sections 2.2 and 2.3, page 136).".

Indeed, the Gentschev reference discloses a recombinant attenuated bacterium comprising an additional gene encoding a different foreign antigenic protein.

US'538 discloses a system for delivery of DNA and antigens into cells, comprising bacteria that enter mammalian cells and rupture, delivering functional plasmid DNA and antigens into the cell cytoplasm. The bacterial strain as disclosed in US'538 may be non-virulent:

> "The strain does not need to be virulent" (column 5, line 43).

Indeed, US'538 Patent recognizes that an antigen delivery (vaccine) system may indeed include a non-virulent bacterial strain.

Bielecki discloses a recombinant Bacillus subtilis bacterium expressing LLO from an inducible heterologous promoter:

> "The structural gene for the LM haemolysin, hlyA, was cloned... into the HindIII site of the plasmid pAG58-ble-1.... This expression cassette was then integrated into the chromosome of a... mutant of B. subtilis" (page 175, second column, first paragraph).

Indeed, the Bielecki reference recognizes that the expressed gene is operably linked to a heterologous promoter.

Bielecki discloses a recombinant Bacillus subtilis bacterium expressing LLO from an inducible heterologous promoter:

> "The structural gene for the LM haemolysin, hlyA, was cloned... into the HindIII site of the plasmid pAG58-ble-1.... This expression cassette was then integrated into the chromosome of a... mutant of B. subtilis" (page 175, second column, first paragraph).

Indeed, the Bielky reference recognizes that the expressed gene is operably linked to a heterologous promoter.

Schmidt provides that E. coli hemolysin is antigenic:

> "Nineteen of the 20 serum samples from patients with O157-associated HUS reacted with the EHEC hemolysin" (last paragraph, page 1058).

Indeed, the Schmidt reference shows that the antigenicity of hemolysin from E. coli is an inherent property of this protein.

Hess provides that E. coli hemolysin is antigenic:

> "the direct transfer of the cytolysin Hly to BCG improved the capacity of this vaccine to efficaciously

stimulate MHC class I-restricted CD8 T cells" (first paragraph, page 5304).

Indeed, the Hess reference recognizes the effective use of a cytolysin to deliver an antigenic protein fragment to immune cells.

Dietrich discloses a Listeria strain, Δ2 that comprises a lysin gene.

"we used attenuated L. monocytogenes cells, which undergo self-destruction in the cytosol of infected macrophages by the production of a P_{actA}-dependent phage lysin" (second paragraph, page 181).

Indeed, the Dietrich reference discloses the use of autolysin to deliver bacterial contents into of macrophages.

IV. CLAIMS 1-42 OF the '556 PATENT ARE ANTICIPATED AND/OR OBVIOUS

1. A substantial new question of patentability as to claim 1 is raised by the Gentschev reference

Claims 1 of the '556 Patent is anticipated under 35 U.S.C. 102(b), in view of the Gentschev reference and is thus unpatentable.

Specifically, in regard to claim 1 as shown in the chart below, every element and limitation of method claim 1 is found in the Gentschev reference. Claim 1 of the '556 Patent recites: "A vaccine comprising a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding a different foreign antigenic agent".

Claim 1 of the '556 Patent	Gentschev Reference
"A vaccine"	**Gentschev** disclosed the use of their bacterial strains for vaccination (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.

Claim 1 of the '556 Patent	Gentschev Reference
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).

2. A substantial new question of patentability as to claim 1 is raised by the Gentschev reference

Claim 1 of the '556 Patent is obvious under 35 U.S.C. 103, over the Gentschev reference and is thus unpatentable.

Specifically, in regard to claim 1 as shown in the chart below, every element and limitation of method claim 1 is found in the Gentschev reference. Claim 1 of the '556 Patent recites: "A vaccine comprising a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding a different foreign antigenic agent".

Claim 1 of the '556 Patent	Gentschev Reference
"A vaccine"	**Gentschev** disclosed the use of their bacterial strains for vaccination (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted,

Claim 1 of the '556 Patent	Gentschev Reference
	functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain.

3. A substantial new question of patentability as to claim 1 is raised by the Gentschev reference in view of the Hess reference

Claim 1 of the '556 Patent is obvious under 35 U.S.C. 103, over the Gentschev reference in view of the Hess reference and is thus unpatentable.

Specifically, in regard to claim 1 as shown in the chart below, every element and limitation of method claim 1 is found in the Gentschev reference and the Hess reference. Claim 1 of the '556 Patent recites: "A vaccine comprising a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding a different foreign antigenic agent".

Claim 1 of the '556 Patent	Gentschev Reference
"A vaccine"	**Hess** disclosed the use of their bacterial strains in vaccines (last paragraph, Introduction section).

Claim 1 of the '556 Patent	Gentschev Reference
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).
Hess disclosed the use of a cytolysin to deliver an antigenic protein (last paragraph, abstract).	

It would have been obvious to one skilled in the art at the time of filing of the '556 Patent to combine the disclosures of Hess and Gentschev, to utilize the bacterial strain of Gentschev in a vaccine.

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain.

In addition, Hess disclosed the use of a cytolysin to deliver an antigenic protein, ovalbumin, to eukaryote cells. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Hess and Gentschev to substitute ovalbumin for the HlyB and HIyD proteins of Gentschev et al. The disclosure of the utility for vaccine applications of the methods of Gentschev and Hess (last paragraph, abstract) would provide the motivation to combine the two references.

4. A substantial new question of patentability as to claim 1 is raised by the Gentschev reference in view of US'538 Patent

Claim 1 of the '556 Patent is obvious under 35 U.S.C. 103, over the Gentschev reference in view of US'538 Patent and is thus unpatentable.

Specifically, in regard to claim 1 as shown in the chart below, every element and limitation of method claim 1 is found in the Gentschev reference and US'538 Patent. Claim 1 of the '556 Patent recites: "A vaccine comprising a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding a different foreign antigenic agent".

Claim 1 of the '556 Patent	Gentschev Reference
"A vaccine"	**Gentschev** disclosed the use of their bacterial strains for vaccination (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**US'538** discloses a strain that does not need to be virulent" (column 5, line 43).
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain.

Additionally, it would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine US'538 Patent with Gentschev to utilize a non-virulent bacterial strain in the method of Gentschev. US'538 Patent and Gentschev both disclose antigen delivery (vaccine) systems, which would provide the motivation to combine the two references.

5. A substantial new question of patentability as to claim 1 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference

Claim 1 of the '556 Patent is obvious under 35 U.S.C. 103, over the Gentschev reference in view of the Bielecki reference and the Hess reference and is thus unpatentable.

Specifically, in regard to claim 1 as shown in the chart below, every element and limitation of method claim 1 is found in the Gentschev reference and the Bielecki reference. Claim 1 of the '556 Patent recites: "A vaccine comprising a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding a different foreign antigenic agent".

Claim 1 of the '556 Patent	Gentschev Reference
"A vaccine"	**Gentschev** disclosed the use of their bacterial strains for vaccination (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Bielecki** discloses a recombinant *Bacillus subtilis* bacterium expressing LLO from an inducible heterologous promoter (page 175, second column, first paragraph).
"which expresses the cytolysin in the	**Gentschev** discloses that the cytolysin is

Claim 1 of the '556 Patent	Gentschev Reference
bacterium"	expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain.

It would have been obvious to one skilled in the art at the time of filing of the '556 Patent to combine Bielecki with Gentschev to obtain the method disclosed in Hess, but utilizing a heterologous promoter to express the cytolysin.

6. A substantial new question of patentability as to claim 1 is raised by the Gentschev reference in view of the Schmidt reference

Claim 1 of the '556 Patent is obvious under 35 U.S.C. 103, over the Gentschev reference in view of the Schmidt reference and is thus unpatentable.

Specifically, in regard to claim 1 as shown in the chart below, every element and limitation of method claim 1 is found in the Gentschev reference. Claim 1 of the '556 Patent recites: "A vaccine comprising a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding a different foreign antigenic agent".

Claim 1 of the '556 Patent	Gentschev Reference
"A vaccine"	**Gentschev** disclosed the use of their bacterial strains for vaccination (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically

Claim 1 of the '556 Patent	Gentschev Reference
	reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).
E. coli hemolysin is antigenic, as evidenced by the **Schmidt** reference (last paragraph, page 1058).	

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain. Schmidt shows that claim 1 claimed elements were inherent in Gentschev.

7. A substantial new question of patentability as to claim 16 is raised by the Gentschev reference

Claim 16 of the '556 Patent is anticipated under 35 U.S.C. 102(b), over the Gentschev reference and is thus unpatentable.

As shown in the chart below, every element and limitation of method claim 1 may be found in the Gentschev reference. Claim 16 of the '556 Patent recites: "A pharmaceutical composition comprising a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which

expresses the cytolysin in the bacterium, and a second gene encoding a different foreign therapeutic agent".

Claim 16 of the '556 Patent	Prior Art Reference
"A pharmaceutical composition"	**Gentschev** disclosed the use of their bacterial strains for vaccination using a pharmaceutical composition comprising same (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).

8. A substantial new question of patentability as to claim 16 is raised by the Gentschev reference

Claim 16 of the '556 Patent is obvious under 35 U.S.C. 103, over the Gentschev reference and is thus unpatentable.

As shown in the chart below, every element and limitation of method claim 1 may be found in the Gentschev reference. Claim 16 of the '556 Patent recites: "A pharmaceutical composition comprising a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding a different foreign therapeutic agent".

Claim 16 of the '556 Patent	Prior Art Reference
"A pharmaceutical composition"	**Gentschev** disclosed the use of their bacterial strains for vaccination using a pharmaceutical composition comprising same (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain

9. A substantial new question of patentability as to claim 16 is raised by the Gentschev reference in view of the Hess reference

Claim 16 of the '556 Patent is obvious under 35 U.S.C. 103, over the Gentschev reference in view of the Hess reference and is thus unpatentable.

As shown in the chart below, every element and limitation of method claim 1 may be found in the Gentschev reference and in the Hess reference. Claim 16 of the '556 Patent recites: "A pharmaceutical composition comprising a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a

heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding a different foreign therapeutic agent".

Claim 16 of the '556 Patent	Prior Art Reference
"A pharmaceutical composition"	**Hess** disclosed the use of their bacterial strains in vaccines using a pharmaceutical composition comprising same (last paragraph, Introduction section).
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).

It would have been obvious to one skilled in the art at the time of filing of the '556 Patent to combine the disclosures of Hess and Gentschev, to utilize the bacterial strain of Gentschev in a pharmaceutical composition. Motivation to do so would be provided by the disclosures by Gentschev and Hess that their bacterial strains have utility as vaccines.

In addition, Hess disclosed the use of a cytolysin to deliver an antigenic protein, ovalbumin, to eukaryote cells. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Hess and Gentschev to substitute ovalbumin for the HlyB and HIyD proteins of Gentschev et al. The disclosure of the utility for vaccine applications of the methods of Gentschev and Hess (last paragraph, abstract) would provide the motivation to combine the two references.

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain.

10. A substantial new question of patentability as to claim 16 is raised by the Gentschev reference in view of US'538 Patent

Claim 16 of the '556 Patent is obvious under 35 U.S.C. 103, over the Gentschev reference in view of US'538 Patent and is thus unpatentable.

As shown in the chart below, every element and limitation of method claim 1 may be found in the Gentschev reference and in US'538 Patent. Claim 16 of the '556 Patent recites: "A pharmaceutical composition comprising a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding a different foreign therapeutic agent".

Claim 16 of the '556 Patent	Prior Art Reference
"A pharmaceutical composition"	**Gentschev** disclosed the use of their bacterial strains for vaccination using a pharmaceutical composition comprising same (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**US'538** discloses a strain that does not need to be virulent" (column 5, line 43).
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain.

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine US'538 Patent with Gentschev to utilize a non-virulent bacterial strain in the method of Gentschev. US'538 Patent and Gentschev both disclose antigen delivery (vaccine) systems, which would provide the motivation to combine the two references.

11. A substantial new question of patentability as to claim 16 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference

Claim 16 of the '815 Patent is obvious under 35 U.S.C. 103, over the Gentschev reference in view of the Bielecki reference and is thus unpatentable.

As shown in the chart below, every element and limitation of method claim 1 may be found in the Gentschev reference and the Bielecki reference. Claim 16 of the '556 Patent recites: "A pharmaceutical composition comprising a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding a different foreign therapeutic agent".

Claim 16 of the '556 Patent	Prior Art Reference
"A pharmaceutical composition"	**Gentschev** disclosed the use of their bacterial strains for vaccination using a pharmaceutical composition comprising same (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first

Claim 16 of the '556 Patent	Prior Art Reference
	paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Bielecki** discloses a recombinant *Bacillus subtilis* bacterium expressing LLO from an inducible heterologous promoter (page 175, second column, first paragraph).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).
Hess disclosed the use of a cytolysin to deliver an antigenic protein (last paragraph, abstract).	

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain.

It would have been obvious to one skilled in the art at the time of filing of the '556 Patent to combine Bielecki with Gentschev to obtain the method disclosed in Hess, but utilizing a heterologous promoter to express the cytolysin.

Alternatively or in addition, Hess disclosed the use of a cytolysin to deliver an antigenic protein, ovalbumin, to eukaryote cells. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Hess and Gentschev to substitute ovalbumin for the HlyB and HIyD proteins of Gentschev et al. The disclosure of the utility for vaccine applications of the methods of Gentschev and Hess (last paragraph, abstract) would provide the motivation to combine the two references.

12. A substantial new question of patentability as to claim 16 is raised by the Gentschev reference in view of the Schmidt reference

Claim 16 of the '815 Patent is obvious under 35 U.S.C. 103, over the Gentschev reference in view of the Schmidt reference and is thus unpatentable.

As shown in the chart below, every element and limitation of method claim 1 may be found in the Gentschev reference. Claim 16 of the '556 Patent recites: "A pharmaceutical composition comprising a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding a different foreign therapeutic agent".

Claim 16 of the '556 Patent	**Prior Art Reference**
"A pharmaceutical composition"	**Gentschev** disclosed the use of their bacterial strains for vaccination using a pharmaceutical composition comprising same (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).
E. coli hemolysin is antigenic, as evidenced by the **Schmidt** reference (last paragraph, page 1058).	

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain. Schmidt shows that the elements of claim 16 were inherent in Gentschev.

13. A substantial new question of patentability as to claim 30 is raised by the Gentschev reference

Claim 30 of the '556 Patent is anticipated under 35 U.S.C. 102(b) over the Gentschev reference and is thus unpatentable.

As shown in the chart below, every element and limitation of method claim 30 is found in the Gentschev reference. Claim 30 of the '556 Patent recites: "A method of introducing a foreign antigenic agent into a eukaryotic cell comprising the step of contacting the cell with a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding the foreign antigenic agent under conditions whereby the agent enters the cell".

Claim 30 of the '556 Patent	Gentschev Reference
"A method of introducing a foreign antigenic agent into a eukaryotic cell comprising the step of contacting the cell with"	**Gentschev** discloses protective immunity in mice against LM, following administration of a recombinant E. coli strain expressing LLO (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).

14. A substantial new question of patentability as to claim 30 is raised by the Gentschev reference

Claim 30 of the '556 Patent is obvious under 35 U.S.C. 103 over the Gentschev reference and is thus unpatentable.

As shown in the chart below, every element and limitation of method claim 30 is found in the Gentschev reference. Claim 30 of the '556 Patent recites: "A method of introducing a foreign antigenic agent into a eukaryotic cell comprising the step of contacting the cell with a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding the foreign antigenic agent under conditions whereby the agent enters the cell".

Claim 30 of the '556 Patent	Gentschev Reference
"A method of introducing a foreign antigenic agent into a eukaryotic cell comprising the step of contacting the cell with"	**Gentschev** discloses protective immunity in mice against LM, following administration of a recombinant E. coli strain expressing LLO (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain.

15. A substantial new question of patentability as to claim 30 is raised by the Gentschev reference in view of the Dietrich reference

Claim 30 of the '556 Patent is obvious under 35 U.S.C. 103 over the Gentschev reference in view of the Dietrich reference and is thus unpatentable.

As shown in the chart below, every element and limitation of method claim 30 is found in the Gentschev reference and the Dietrich reference. Claim 30 of the '556 Patent recites: "A method of introducing a foreign antigenic agent into a eukaryotic cell comprising the step of contacting the cell with a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding the foreign antigenic agent under conditions whereby the agent enters the cell".

Claim 30 of the '556 Patent	Gentschev Reference
"A method of introducing a foreign antigenic agent into a eukaryotic cell comprising the step of contacting the cell with"	**Dietrich** discloses introduction of GFP (foreign agent) into macrophages (host cells) by contacting the macrophages with a mutant Listeria strain, Δ2 that comprises an autolysin (pages 183-184).Gentschev discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted,

Claim 30 of the '556 Patent	Gentschev Reference
	functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).

It would have been obvious to one skilled in the art at the time of filing of the '556 Patent to combine the disclosures of Dietrich and Gentschev, to utilize the bacterial strain of Gentschev to introduce a foreign antigenic agent into a eukaryotic cell.

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain.

16. A substantial new question of patentability as to claim 30 is raised by the Gentschev reference in view of US'538 Patent

Claim 30 of the '556 Patent is obvious under 35 U.S.C. 103 over the Gentschev reference in view of US'538 Patent and is thus unpatentable.

As shown in the chart below, every element and limitation of method claim 30 is found in the Gentschev reference and US'538 Patent. Claim 30 of the '556 Patent recites: "A method of introducing a foreign antigenic agent into a eukaryotic cell comprising the step of contacting the cell with a non-virulent bacterium comprising a first gene encoding a

nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding the foreign antigenic agent under conditions whereby the agent enters the cell".

Claim 30 of the '556 Patent	Gentschev Reference
"A method of introducing a foreign antigenic agent into a eukaryotic cell comprising the step of contacting the cell with"	**Gentschev** discloses protective immunity in mice against LM, following administration of a recombinant E. coli strain expressing LLO (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**US'538** discloses a strain that does not need to be virulent" (column 5, line 43).
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine US'538 Patent with Gentschev to utilize a non-virulent bacterial strain in the method of Gentschev. US'538 Patent and the Gentschev reference both disclose antigen delivery (vaccine) systems, which would provide the motivation to combine the two references.

17. A substantial new question of patentability as to claim 30 is raised by the Gentschev reference in view of the Hess reference and the Bielecki reference

Claim 30 of the '556 Patent is obvious under 35 U.S.C. 103 over the Gentschev reference and is thus unpatentable.

As shown in the chart below, every element and limitation of method claim 30 is found in the Gentschev reference. Claim 30 of the '556 Patent recites: "A method of introducing a foreign antigenic agent into a eukaryotic cell comprising the step of contacting the cell with a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding the foreign antigenic agent under conditions whereby the agent enters the cell".

Claim 30 of the '556 Patent	Gentschev Reference
"A method of introducing a foreign antigenic agent into a eukaryotic cell comprising the step of contacting the cell with"	**Gentschev** discloses protective immunity in mice against LM, following administration of a recombinant E. coli strain expressing LLO (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Bielecki** discloses a recombinant *Bacillus subtilis* bacterium expressing LLO from an inducible heterologous promoter (page 175, second column, first paragraph).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).
Hess disclosed the use of a cytolysin to deliver an antigenic protein (last paragraph, abstract).	

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain.

It would have been obvious to one skilled in the art at the time of filing of the '556 Patent to combine the Bielecki reference with the Gentschev reference to obtain the method disclosed in Hess, but utilizing a heterologous promoter to express the cytolysin.

Additionally, Hess disclosed the use of a cytolysin to deliver an antigenic protein, ovalbumin, to eukaryote cells. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Hess and Gentschev to substitute ovalbumin for the HlyB and HIyD proteins of Gentschev et al. The disclosure of the utility for vaccine applications of the methods of Gentschev and Hess (last paragraph, abstract) would provide the motivation to combine the two references.

18. A substantial new question of patentability as to claim 30 is raised by the Gentschev reference in view of the Schmidt reference

Claim 30 of the '556 Patent is obvious under 35 U.S.C. 103 over the Gentschev in view of the Schmidt reference and is thus unpatentable.

As shown in the chart below, every element and limitation of method claim 30 is found in the Gentschev reference. Claim 30 of the '556 Patent recites: "A method of introducing a foreign antigenic agent into a eukaryotic cell comprising the step of contacting the cell with a non-virulent bacterium comprising a first gene encoding a nonsecreted foreign functional cytolysin operably linked to a heterologous promoter which expresses the cytolysin in the bacterium, and a second gene encoding the foreign antigenic agent under conditions whereby the agent enters the cell".

Claim 30 of the '556 Patent	Gentschev Reference
"A method of introducing a foreign antigenic agent into a eukaryotic cell comprising the step of contacting the cell with"	**Gentschev** discloses protective immunity in mice against LM, following administration of a recombinant E. coli strain expressing LLO (first paragraph, section 2.4, page 137).
"a nonvirulent bacterium"	**Gentschev** describes a mutation that "drastically reduces virulence". "Drastically reduces virulence" and "nonvirulent" are one and the same (page 135, first paragraph.
"comprising a first gene encoding a nonsecreted foreign functional cytolysin"	**Gentschev's** bacterium comprises hly gene of L. monocytogenes EGD thus, non-secreted, functional cytolysins were utilized (first paragraph, section 2.4, page 137).
"operably linked to a heterologous promoter"	**Gentschev** discloses a non-secreted foreign functional expressed from several different non-Salmonella promoters, phlyI and plac (first paragraph, section 2.2, page 135).
"which expresses the cytolysin in the bacterium"	**Gentschev** discloses that the cytolysin is expressed in the bacterium (first paragraph, section 2.2, page 135).
"and a second gene encoding a different foreign antigenic agent"	**Gentschev** discloses that the recombinant attenuated bacteria further comprise the genes hlyC, hlyB and hlyD (first paragraph, section 2.2, page 135).
E. coli hemolysin is antigenic, as evidenced by the **Schmidt** reference (last paragraph, page 1058).	

It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent in view of Gentschev to substitute a non-virulent bacterial strain for the attenuated bacterial strains disclosed in Gentschev. The desire to improve the safety of the method of Gentschev would provide the motivation to utilize a non-virulent bacterial strain. Schmidt shows that the elements in claim 30 were inherent in the Gentschev reference.

19. A substantial new question of patentability as to claims 2 and 17 is raised by the Gentschev reference

Claims 2 and 17 of the '556 Patent are dependent on claims 1 and 16, respectively, and are anticipated under 35 U.S.C.102 (b), over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 2 and 17 is found in the Gentschev reference. Claims 2 and 17 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is absent a functional signal sequence" and "The composition of claim 16, wherein the cytolysin is absent a functional signal sequence", respectively.

Claims 2 and 17 of the '556 Patent	Gentschev reference
"the cytolysin is absent a functional signal sequence "	**Gentschev** provides that the LLO protein comprised in the bacteria lacked its N-terminal signal peptide (see legend to Table 1, page 136).

The Gentschev reference provides a bacterial produced LLO protein lacking a signal sequence thus the Gentschev reference anticipates claims 2 and 17 reciting that a cytolysin is absent a functional signal sequence.

20. A substantial new question of patentability as to claims 2 and 17 is raised by the Gentschev reference

Claims 2 and 17 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 2 and 17 is found in the Gentschev reference. Claims 2 and 17 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is absent a functional signal sequence" and "The composition of claim 16, wherein the cytolysin is absent a functional signal sequence", respectively.

Claims 2 and 17 of the '556 Patent	Gentschev reference
"the cytolysin is absent a functional signal sequence "	**Gentschev** provides that the LLO protein comprised in the bacteria lacked its N-terminal signal peptide (see legend to Table 1, page 136).

21. A substantial new question of patentability as to claims 2 and 17 is raised by the Gentschev reference in view of the Hess reference

Claims 2 and 17 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 2 and 17 is found in the Gentschev reference. Claims 2 and 17 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is absent a functional signal sequence" and "The composition of claim 16, wherein the cytolysin is absent a functional signal sequence", respectively.

Claims 2 and 17 of the '556 Patent	Gentschev reference
"the cytolysin is absent a functional signal sequence "	**Gentschev** provides that the LLO protein comprised in the bacteria lacked its N-terminal signal peptide (see legend to Table 1, page 136).

22. A substantial new question of patentability as to claims 2 and 17 is raised by the Gentschev reference in view of the US'538 Patent

Claims 2 and 17 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 2 and 17 is found in the Gentschev reference. Claims 2 and 17 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is absent a functional signal sequence" and "The composition of claim 16, wherein the cytolysin is absent a functional signal sequence", respectively.

Claims 2 and 17 of the '556 Patent	Gentschev reference
"the cytolysin is absent a functional signal sequence "	**Gentschev** provides that the LLO protein comprised in the bacteria lacked its N-terminal signal peptide (see legend to Table 1, page 136).

23. A substantial new question of patentability as to claims 2 and 17 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference

Claims 2 and 17 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 2 and 17 is found in the Gentschev reference. Claims 2 and 17 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is absent a functional signal sequence" and "The composition of claim 16, wherein the cytolysin is absent a functional signal sequence", respectively.

Claims 2 and 17 of the '556 Patent	Gentschev reference
"the cytolysin is absent a functional signal sequence "	**Gentschev** provides that the LLO protein comprised in the bacteria lacked its N-terminal signal peptide (see legend to Table 1, page 136).

24. A substantial new question of patentability as to claims 2 and 17 is raised by the Gentschev reference in view of the Schmidt reference

Claims 2 and 17 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 2 and 17 is found in the Gentschev reference. Claims 2 and 17 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is absent a functional signal sequence" and "The composition of claim 16, wherein the cytolysin is absent a functional signal sequence", respectively.

Claims 2 and 17 of the '556 Patent	Gentschev reference
"the cytolysin is absent a functional signal sequence "	**Gentschev** provides that the LLO protein comprised in the bacteria lacked its N-terminal signal peptide (see legend to Table 1, page 136).

25. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference

Claims 3 and 18 of the '556 Patent are dependent on claims 1 and 16, respectively, and are anticipated under 35 U.S.C.102 (b), over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 3 and 18 is found in the Gentschev reference. Claims 3 and 18 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is listeriolysin" and "The composition of claim 16, wherein the cytolysin is listeriolysin", respectively.

Claims 3 and 18 of the '556 Patent	Gentschev reference
"the cytolysin is listeriolysin"	**Gentschev** discloses expression of LLO in a recombinant Salmonella strain (first paragraph, section 2.3, page 136).

The disclosure provided in Gentschev provides a Salmonella strain expressing LLO. Thus, Gentschev anticipates claims 3 and 18 reciting a cytolysin that is listeriolysin.

26. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference

Claims 3 and 18 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 3 and 18 is found in the Gentschev reference. Claims 3 and 18 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is listeriolysin" and "The composition of claim 16, wherein the cytolysin is listeriolysin", respectively.

Claims 3 and 18 of the '556 Patent	Gentschev reference
"the cytolysin is listeriolysin"	**Gentschev** discloses expression of LLO in a recombinant Salmonella strain (first paragraph, section 2.3, page 136).

27. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference in view of the Hess reference

Claims 3 and 18 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 3 and 18 is found in the Gentschev reference. Claims 3 and 18 of the '556 Patent recite: "The vaccine of claim 1,

wherein the cytolysin is listeriolysin" and "The composition of claim 16, wherein the cytolysin is listeriolysin", respectively.

Claims 3 and 18 of the '556 Patent	Gentschev reference
"the cytolysin is listeriolysin"	**Gentschev** discloses expression of LLO in a recombinant Salmonella strain (first paragraph, section 2.3, page 136).

28. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference in view of the US'538 Patent

Claims 3 and 18 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 3 and 18 is found in the Gentschev reference. Claims 3 and 18 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is listeriolysin" and "The composition of claim 16, wherein the cytolysin is listeriolysin", respectively.

Claims 3 and 18 of the '556 Patent	Gentschev reference
"the cytolysin is listeriolysin"	**Gentschev** discloses expression of LLO in a recombinant Salmonella strain (first paragraph, section 2.3, page 136).

29. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference

Claims 3 and 18 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 3 and 18 is found in the Gentschev reference. Claims 3 and 18 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is listeriolysin" and "The composition of claim 16, wherein the cytolysin is listeriolysin", respectively.

Claims 3 and 18 of the '556 Patent	Gentschev reference
"the cytolysin is listeriolysin"	**Gentschev** discloses expression of LLO in a recombinant Salmonella strain (first paragraph, section 2.3, page 136).

30. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference in view of the Schmidt reference

Claims 3 and 18 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 3 and 18 is found in the Gentschev reference. Claims 3 and 18 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is listeriolysin" and "The composition of claim 16, wherein the cytolysin is listeriolysin", respectively.

Claims 3 and 18 of the '556 Patent	Gentschev reference
"the cytolysin is listeriolysin"	**Gentschev** discloses expression of LLO in a recombinant Salmonella strain (first paragraph, section 2.3, page 136).

31. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference and the Bielecki reference

Claims 3 and 18 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Bielecki reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 3 and 18 is found in the Bielecki reference. Claims 3 and 18 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is listeriolysin" and "The composition of claim 16, wherein the cytolysin is listeriolysin", respectively.

Claims 3 and 18 of the '556 Patent	Bielecki reference
"the cytolysin is listeriolysin"	**Bielecki** describes production of LLO by a heterologous bacterial species (page 175, second column, first paragraph).

32. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference and the Bielecki reference

Claims 3 and 18 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Bielecki reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 3 and 18 is found in the Bielecki reference. Claims 3 and 18 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is listeriolysin" and "The composition of claim 16, wherein the cytolysin is listeriolysin", respectively.

Claims 3 and 18 of the '556 Patent	Bielecki reference
"the cytolysin is listeriolysin"	**Bielecki** describes production of LLO by a heterologous bacterial species (page 175, second column, first paragraph).

33. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference and the Bielecki reference in view of the Hess reference

Claims 3 and 18 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Bielecki reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 3 and 18 is found in the Bielecki reference. Claims 3 and 18 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is listeriolysin" and "The composition of claim 16, wherein the cytolysin is listeriolysin", respectively.

Claims 3 and 18 of the '556 Patent	Bielecki reference
"the cytolysin is listeriolysin"	**Bielecki** describes production of LLO by a heterologous bacterial species (page 175, second column, first paragraph).

34. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference and the Bielecki reference in view of the US'538 Patent

Claims 3 and 18 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Bielecki reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 3 and 18 is found in the Bielecki reference. Claims 3 and 18 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is listeriolysin" and "The composition of claim 16, wherein the cytolysin is listeriolysin", respectively.

Claims 3 and 18 of the '556 Patent	Bielecki reference
"the cytolysin is listeriolysin"	**Bielecki** describes production of LLO by a heterologous bacterial species (page 175, second column, first paragraph).

35. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference and the Bielecki reference in view of the Bielecki reference and the Hess reference

Claims 3 and 18 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Bielecki reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 3 and 18 is found in the Bielecki reference. Claims 3 and 18 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is listeriolysin" and "The composition of claim 16, wherein the cytolysin is listeriolysin", respectively.

Claims 3 and 18 of the '556 Patent	Bielecki reference
"the cytolysin is listeriolysin"	**Bielecki** describes production of LLO by a heterologous bacterial species (page 175, second column, first paragraph).

36. A substantial new question of patentability as to claims 3 and 18 is raised by the Gentschev reference and the Bielecki reference in view of the Schmidt reference

Claims 3 and 18 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Bielecki reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 3 and 18 is found in the Bielecki reference. Claims 3 and 18 of the '556 Patent recite: "The vaccine of claim 1, wherein the cytolysin is listeriolysin" and "The composition of claim 16, wherein the cytolysin is listeriolysin", respectively.

Claims 3 and 18 of the '556 Patent	Bielecki reference
"the cytolysin is listeriolysin"	**Bielecki** describes production of LLO by a heterologous bacterial species (page 175, second column, first paragraph).

37. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference and the Dietrich reference

Claims 4 and 19 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference, and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are anticipated under 35 U.S.C.102(b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 4 and 19 are found in the Dietrich reference. Claims 4 and 19 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin" and "The composition of claim 16, wherein the bacterium further

comprises a third gene encoding an invasin and a fourth gene encoding an autolysin", respectively.

Claims 4 and 19 of the '556 Patent	Dietrich reference
"the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin"	**Dietrich** discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin (page 181).

Dietrich discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin. Dietrich is directed to the delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide LM. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Dietrich and Gentschev to substitute a strain comprising an autolysin for the HlyB and HIyD proteins of Gentschev. The disclosure of the utility for vaccine applications of the methods of Gentschev and Dietrich would provide the motivation to combine the two references. Further, Gentschev and Dietrich provide an expectation of success in achieving therapeutic efficacy.

38. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference and the Dietrich reference

Claims 4 and 19 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference, and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 4 and 19 are found in the Dietrich reference. Claims 4 and 19 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin" and "The composition of claim 16, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin", respectively.

Claims 4 and 19 of the '556 Patent	Dietrich reference
"the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin"	**Dietrich** discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin (page 181).

Dietrich discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin. Dietrich is directed to the delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide LM. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Dietrich and Gentschev to substitute a strain comprising an autolysin for the HlyB and HIyD proteins of Gentschev. The disclosure of the utility for vaccine applications of the methods of Gentschev and Dietrich would provide the motivation to combine the two references. Further, Gentschev and Dietrich provide an expectation of success in achieving therapeutic efficacy.

39. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference

Claims 4 and 19 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 4 and 19 are found in the Dietrich reference. Claims 4 and 19 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin" and "The composition of claim 16, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin", respectively.

Claims 4 and 19 of the '556 Patent	Dietrich reference
"the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin"	**Dietrich** discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin (page 181).

Dietrich discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin. Dietrich is directed to the delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide LM. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Dietrich, Hess, and Gentschev to substitute a strain comprising an autolysin for the HlyB and HIyD proteins of Gentschev. The disclosure of the utility for vaccine applications of the methods of Gentschev, Hess, and Dietrich would provide the motivation to combine the two references. Further, Gentschev and Dietrich provide an expectation of success in achieving therapeutic efficacy.

40. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference and the Dietrich reference in view of US'538 Patent

Claims 4 and 19 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 4 and 19 are found in the Dietrich reference. Claims 4 and 19 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin" and "The composition of claim 16, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin", respectively.

Claims 4 and 19 of the '556 Patent	Dietrich reference
"the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin"	**Dietrich** discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin (page 181).

Dietrich discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin. Dietrich is directed to the delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide LM. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Dietrich, US'538 Patent, and Gentschev to substitute a strain comprising an autolysin for the HlyB and HIyD proteins of Gentschev. The disclosure of the utility for vaccine applications of the methods of Gentschev, US'538 Patent, and Dietrich would provide the motivation to combine the two references. Further, Gentschev and Dietrich provide an expectation of success in achieving therapeutic efficacy.

41. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference

Claims 4 and 19 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 4 and 19 are found in the Dietrich reference. Claims 4 and 19 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin" and "The composition of claim 16, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin", respectively.

Claims 4 and 19 of the '556 Patent	Dietrich reference
"the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin"	**Dietrich** discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin (page 181).

Dietrich discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin. Dietrich is directed to the delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide LM. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Dietrich, Bielecki, Hess, and Gentschev to substitute a strain comprising an autolysin for the HlyB and HIyD proteins of Gentschev. The disclosure of the utility for vaccine applications of the methods of Gentschev, Bielecki, Hess, and Dietrich would provide the motivation to combine the two references. Further, Gentschev and Dietrich provide an expectation of success in achieving therapeutic efficacy.

42. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference

Claims 4 and 19 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Schmidt and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 4 and 19 are found in the Dietrich reference. Claims 4 and 19 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin" and "The composition of claim 16, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin", respectively.

Claims 4 and 19 of the '556 Patent	Dietrich reference
"the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin"	**Dietrich** discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin (page 181).

Dietrich discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin. Dietrich is directed to the delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide LM. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Dietrich, Schmidt, and Gentschev to substitute a strain comprising an autolysin for the HlyB and HIyD proteins of Gentschev. The disclosure of the utility for vaccine applications of the methods of Gentschev, Schmidt, and Dietrich would provide the motivation to combine the two references. Further, Gentschev and Dietrich provide an expectation of success in achieving therapeutic efficacy.

43. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference, the Dietrich reference, and the Galan reference

Claims 4 and 19 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference the Dietrich reference, and the Galan reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 4 and 19 are found in the Galan reference and the Dietrich reference. Claims 4 and 19 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin" and "The composition of claim 16, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin", respectively.

Claims 4 and 19 of the '556 Patent	Prior Art reference
"the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin "	**Dietrich** discloses a Listeria strain, Δ2 that comprises an autolysin (page 181). **Galan** shows that a Salmonella bacterium contains invasin proteins (Galan JE, Ginocchio C, Costeas P. Molecular and functional characterization of the Salmonella invasion gene invA: homology of InvA to members of a new protein family. J. Bacteriol. 1992 Jul;174(13):4338-49.(Exhibit G)).

Dietrich discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin. Galan shows that a Salmonella bacterium contains invasin proteins. Thus, the aroA mutant strains of Gentschev express invasin. Dietrich is directed to the delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide LM. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Dietrich and Gentschev to substitute a strain comprising an autolysin for the HlyB and HIyD proteins of Gentschev. The disclosure of the utility for vaccine applications of the methods of Gentschev and Dietrich would provide the motivation to combine the two references. Further, Gentschev and Dietrich provide an expectation of success in achieving therapeutic efficacy.

44. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference, the Dietrich reference, and the Galan reference

Claims 4 and 19 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference the Dietrich reference, and the Galan reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 4 and 19 are found in the Galan reference and the Dietrich reference. Claims 4 and 19 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin" and "The composition of claim 16, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin", respectively.

Claims 4 and 19 of the '556 Patent	**Prior Art reference**
"the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin "	**Dietrich** discloses a Listeria strain, Δ2 that comprises an autolysin (page 181). **Galan** shows that a Salmonella bacterium contains invasin proteins (Galan JE, Ginocchio C, Costeas P. Molecular and functional characterization of the Salmonella invasion gene invA: homology of InvA to members of a new protein family. J. Bacteriol. 1992 Jul;174(13):4338-49.(Exhibit G)).

Dietrich discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin. Galan shows that a Salmonella bacterium contains invasin proteins. Thus, the aroA mutant strains of Gentschev express invasin. Dietrich is directed to the delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide LM. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Dietrich and Gentschev to substitute a strain comprising an autolysin for the HlyB and HIyD proteins of Gentschev. The disclosure of the utility for vaccine applications of the methods of Gentschev and Dietrich would provide the motivation to combine the two references. Further, Gentschev and Dietrich provide an expectation of success in achieving therapeutic efficacy.

45. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference, the Dietrich reference, and the Galan reference in view of the Hess reference

Claims 4 and 19 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference the Dietrich reference, and the Galan reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 4 and 19 are found in the Galan reference and the Dietrich reference. Claims 4 and 19 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin" and "The composition of claim 16, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin", respectively.

Claims 4 and 19 of the '556 Patent	Prior Art reference
"the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin "	**Dietrich** discloses a Listeria strain, Δ2 that comprises an autolysin (page 181). **Galan** shows that a Salmonella bacterium contains invasin proteins (Galan JE, Ginocchio C, Costeas P. Molecular and functional characterization of the Salmonella invasion gene invA: homology of InvA to members of a new protein family. J. Bacteriol. 1992 Jul;174(13):4338-49.(Exhibit G)).

Dietrich discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin. Galan shows that a Salmonella bacterium contains invasin proteins. Thus, the aroA mutant strains of Gentschev express invasin. Dietrich is directed to the delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide LM. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Dietrich, Hess, and Gentschev to substitute a strain comprising an autolysin for the HlyB and HIyD proteins of Gentschev. The disclosure of the utility for vaccine applications of the methods of Gentschev, Hess, and Dietrich would provide the motivation to combine the two references. Further, Gentschev and Dietrich provide an expectation of success in achieving therapeutic efficacy.

46. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference, the Dietrich reference, and the Galan reference in view of US'538 Patent

Claims 4 and 19 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference the Dietrich reference, and the Galan reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 4 and 19 are found in the Galan reference and the Dietrich reference. Claims 4 and 19 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin" and "The composition of claim 16, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin", respectively.

Claims 4 and 19 of the '556 Patent	**Prior Art reference**
"the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin "	**Dietrich** discloses a Listeria strain, Δ2 that comprises an autolysin (page 181). **Galan** shows that a Salmonella bacterium contains invasin proteins (Galan JE, Ginocchio C, Costeas P. Molecular and functional characterization of the Salmonella invasion gene invA: homology of InvA to members of a new protein family. J. Bacteriol. 1992 Jul;174(13):4338-49.(Exhibit G)).

Dietrich discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin. Galan shows that a Salmonella bacterium contains invasin proteins. Thus, the aroA mutant strains of Gentschev express invasin. Dietrich is directed to the delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide LM. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Dietrich, US'538 Patent, and Gentschev to substitute a strain comprising an autolysin for the HlyB and HIyD proteins of Gentschev. The disclosure of the utility for vaccine applications of the methods of Gentschev, US'538 Patent, and Dietrich would provide the motivation to combine the two references. Further, Gentschev and Dietrich provide an expectation of success in achieving therapeutic efficacy.

47. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference, the Dietrich reference, and the Galan reference in view of the Bielecki reference and the Hess reference

Claims 4 and 19 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference the Dietrich reference, and the Galan reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 4 and 19 are found in the Galan reference and the Dietrich reference. Claims 4 and 19 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin" and "The composition of claim 16, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin", respectively.

Claims 4 and 19 of the '556 Patent	Prior Art reference
"the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin "	**Dietrich** discloses a Listeria strain, Δ2 that comprises an autolysin (page 181). **Galan** shows that a Salmonella bacterium contains invasin proteins (Galan JE, Ginocchio C, Costeas P. Molecular and functional characterization of the Salmonella invasion gene invA: homology of InvA to members of a new protein family. J. Bacteriol. 1992 Jul;174(13):4338-49.(Exhibit G)).

Dietrich discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin. Galan shows that a Salmonella bacterium contains invasin proteins. Thus, the aroA mutant strains of Gentschev express invasin. Dietrich is directed to the delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide LM. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Dietrich, Bielecki, Hess, and Gentschev to substitute a strain comprising an autolysin for the HlyB and HIyD proteins of Gentschev. The disclosure of the utility for vaccine applications of the methods of Gentschev, Bielecki, Hess, and Dietrich would provide the motivation to combine the two references. Further, Gentschev and Dietrich provide an expectation of success in achieving therapeutic efficacy.

48. A substantial new question of patentability as to claims 4 and 19 is raised by the Gentschev reference, the Dietrich reference, and the Galan reference in view of the Schmidt reference

Claims 4 and 19 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference the Dietrich reference, and the Galan reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 4 and 19 are found in the Galan reference and the Dietrich reference. Claims 4 and 19 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin" and "The composition of claim 16, wherein the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin", respectively.

Claims 4 and 19 of the '556 Patent	**Prior Art reference**
"the bacterium further comprises a third gene encoding an invasin and a fourth gene encoding an autolysin "	**Dietrich** discloses a Listeria strain, Δ2 that comprises an autolysin (page 181). **Galan** shows that a Salmonella bacterium contains invasin proteins (Galan JE, Ginocchio C, Costeas P. Molecular and functional characterization of the Salmonella invasion gene invA: homology of InvA to members of a new protein family. J. Bacteriol. 1992 Jul;174(13):4338-49.(Exhibit G)).

Dietrich discloses a Listeria strain, Δ2 that comprises an invasin and an autolysin. Galan shows that a Salmonella bacterium contains invasin proteins. Thus, the aroA mutant strains of Gentschev express invasin. Dietrich is directed to the delivery of antigen-encoding plasmid DNA into the cytosol of macrophages by attenuated suicide LM. It would have been obvious to one skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Dietrich, Schmidt, and Gentschev to substitute a strain comprising an autolysin for the HlyB and HIyD proteins of Gentschev. The disclosure of the utility for vaccine applications of the methods of Gentschev, Schmidt, and Dietrich would provide the motivation to combine the two references. Further, Gentschev and Dietrich provide an expectation of success in achieving therapeutic efficacy.

49. A substantial new question of patentability as to claims 5 and 20 is raised by the Gentschev reference

Claims 5 and 20 of the '556 Patent are dependent on claims 1 and 16, respectively, and are anticipated under 35 U.S.C.102 (b), over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 5 and 20 is found in the Gentschev reference. Claims 5 and 20 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli" and "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli", respectively.

Claims 5 and 20 of the '556 Patent	Gentschev reference
"the bacterium is a laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).

The laboratory E. coli strain described in Gentschev is a laboratory strain of E. coli. Thus Gentschev anticipates claims 5 and 20 reciting a laboratory strain of E. coli.

50. A substantial new question of patentability as to claims 5 and 20 is raised by the Gentschev reference

Claims 5 and 20 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 5 and 20 is found in the Gentschev reference. Claims 5 and 20 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli" and "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli", respectively.

Claims 5 and 20 of the '556 Patent	Gentschev reference
"the bacterium is a laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).

51. A substantial new question of patentability as to claims 5 and 20 is raised by the Gentschev reference in view of the Hess reference

Claims 5 and 20 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 5 and 20 is found in the Gentschev reference. Claims 5 and 20 of the '556 Patent recite: "The vaccine of claim 1,

wherein the bacterium is a laboratory strain of E. coli" and "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli", respectively.

Claims 5 and 20 of the '556 Patent	Gentschev reference
"the bacterium is a laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).

52. A substantial new question of patentability as to claims 5 and 20 is raised by the Gentschev reference in view of the US'538 Patent

Claims 5 and 20 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 5 and 20 is found in the Gentschev reference. Claims 5 and 20 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli" and "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli", respectively.

Claims 5 and 20 of the '556 Patent	Gentschev reference
"the bacterium is a laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).

53. A substantial new question of patentability as to claims 5 and 20 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference

Claims 5 and 20 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 5 and 20 is found in the Gentschev reference. Claims 5 and 20 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli" and "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli", respectively.

Claims 5 and 20 of the '556 Patent	Gentschev reference
"the bacterium is a laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).

54. A substantial new question of patentability as to claims 5 and 20 is raised by the Gentschev reference in view of the Schmidt reference

Claims 5 and 20 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 5 and 20 is found in the Gentschev reference. Claims 5 and 20 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli" and "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli", respectively.

Claims 5 and 20 of the '556 Patent	Gentschev reference
"the bacterium is a laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).

55. A substantial new question of patentability as to claims 6, 21, and 32 is raised by the Gentschev reference and the Dietrich reference

Claims 6, 21, and 32 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 6, 21, and 32 is found in the Dietrich reference. Claims 6, 21, and 32 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable", "The composition of claim 16, wherein the bacterium is dead or non-viable" and "The method of claim 30, wherein the bacterium is dead or non-viable", respectively.

Claims 6, 21, and 32 of the '556 Patent	**Dietrich reference**
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).

56. A substantial new question of patentability as to claims 6, 21, and 32 is raised by the Gentschev reference and the Dietrich reference

Claims 6, 21, and 32 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 6, 21, and 32 is found in the Dietrich reference. Claims 6, 21, and 32 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable", "The composition of claim 16,

wherein the bacterium is dead or non-viable" and "The method of claim 30, wherein the bacterium is dead or non-viable", respectively.

Claims 6, 21, and 32 of the '556 Patent	Dietrich reference
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).

57. A substantial new question of patentability as to claims 6, 21, and 32 is raised by the Gentschev reference and the Dietrich reference in view of US'538 Patent

Claims 6, 21, and 32 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 6, 21, and 32 is found in the Dietrich reference. Claims 6, 21, and 32 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable", "The composition of claim 16, wherein the bacterium is dead or non-viable" and "The method of claim 30, wherein the bacterium is dead or non-viable", respectively.

Claims 6, 21, and 32 of the '556 Patent	Dietrich reference
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).

58. A substantial new question of patentability as to claims 6, 21, and 32 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference and the Bielecki reference

Claims 6, 21, and 32 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Hess reference and the Bielecki reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

As shown in the chart below, the element and limitation of claims 6, 21, and 32 is found in the Dietrich reference. Claims 6, 21, and 32 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable", "The composition of claim 16, wherein the bacterium is dead or non-viable" and "The method of claim 30, wherein the bacterium is dead or non-viable", respectively.

Claims 6, 21, and 32 of the '556 Patent	**Dietrich reference**
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).

59. A substantial new question of patentability as to claims 6 and 21 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference

Claims 6 and 21 of the '556 Patent are dependent on claims 1 and 16 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 anticipated under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

As shown in the chart below, the element and limitation of claims 6 and 21 is found in the Dietrich reference. Claims 6 and 21 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable", "The composition of claim 16, wherein the bacterium is dead or non-viable" and "The method of claim 30, wherein the bacterium is dead or non-viable", respectively.

Claims 6 and 21 of the '556 Patent	Dietrich reference
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).

60. A substantial new question of patentability as to claim 32 is raised by the Gentschev reference and the Dietrich reference in view of the Dietrich reference

Claim 32 of the '556 Patent are dependent on claim 30, and is obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is anticipated under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 32 is found in the Dietrich reference. Claim 32 of the '556 Patent recites: "The method of claim 30, wherein the bacterium is dead or non-viable", respectively.

Claims 6, 21, and 32 of the '556 Patent	Dietrich reference
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).

61. A substantial new question of patentability as to claims 6, 21, and 32 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference

Claims 6, 21, and 32 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Schmidt and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 6, 21, and 32 is found in the Dietrich reference. Claims 6, 21, and 32 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable", "The composition of claim 16, wherein the bacterium is dead or non-viable" and "The method of claim 30, wherein the bacterium is dead or non-viable", respectively.

Claims 6, 21, and 32 of the '556 Patent	**Dietrich reference**
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).

62. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference

Claims 7, 22, and 33 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are anticipated under 35 U.S.C.102 (b), over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 7, 22, and 33 is found in the Gentschev reference. Claims 7, 22, and 33 of the '556 Patent recites: "The

vaccine of claim 1, wherein the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium comprises the cytolysin " and "The method of claim 30, wherein the bacterium comprises the cytolysin ", respectively.

Claims 7, 22 and 33 of the '556 Patent	Prior Art reference
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

63. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference

Claims 7, 22, and 33 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 7, 22, and 33 is found in the Gentschev reference. Claims 7, 22, and 33 of the '556 Patent recites: "The vaccine of claim 1, wherein the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium comprises the cytolysin " and "The method of claim 30, wherein the bacterium comprises the cytolysin ", respectively.

Claims 7, 22 and 33 of the '556 Patent	Prior Art reference
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

64. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference in view of US'538 Patent

Claims 7, 22, and 33 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 7, 22, and 33 is found in the Gentschev reference. Claims 7, 22, and 33 of the '556 Patent recites: "The vaccine of claim 1, wherein the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium comprises the cytolysin " and "The method of claim 30, wherein the bacterium comprises the cytolysin ", respectively.

Claims 7, 22 and 33 of the '556 Patent	Prior Art reference
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

65. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference in view of the Hess reference and the Bielecki reference

Claims 7, 22, and 33 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and the Bielecki reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

As shown in the chart below, the element and limitation of claims 7, 22, and 33 is found in the Gentschev reference. Claims 7, 22, and 33 of the '556 Patent recites: "The

vaccine of claim 1, wherein the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium comprises the cytolysin " and "The method of claim 30, wherein the bacterium comprises the cytolysin ", respectively.

Claims 7, 22 and 33 of the '556 Patent	Prior Art reference
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

66. A substantial new question of patentability as to claims 7 and 22 is raised by the Gentschev reference in view of the Hess reference

Claims 7 and 22 of the '556 Patent are dependent on claims 1 and 16 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claim 1 and 16 are anticipated under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

As shown in the chart below, the element and limitation of claims 7 and 22 is found in the Gentschev reference. Claims 7 and 22 of the '556 Patent recites: "The vaccine of claim 1, wherein the bacterium comprises the cytolysin" and "The composition of claim 16, wherein the bacterium comprises the cytolysin", respectively.

Claims 7 and 22 of the '556 Patent	Prior Art reference
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

67. A substantial new question of patentability as to claim 33 is raised by the Gentschev reference in view of the Dietrich reference

Claim 33 of the '556 Patent are dependent on claim 30, and is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is anticipated under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 33 is found in the Gentschev reference. Claim 33 of the '556 Patent recites: "The method of claim 30, wherein the bacterium comprises the cytolysin ".

Claim 33 of the '556 Patent	Prior Art reference
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

68. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference in view of the Schmidt reference

Claims 7, 22, and 33 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 7, 22, and 33 is found in the Gentschev reference. Claims 7, 22, and 33 of the '556 Patent recites: "The vaccine of claim 1, wherein the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium comprises the cytolysin " and "The method of claim 30, wherein the bacterium comprises the cytolysin ", respectively.

Claims 7, 22 and 33 of the '556 Patent	Prior Art reference
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

69. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference and the Schmidt reference

Claims 7, 22, and 33 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 7, 22, and 33 is found in the Gentschev reference. Claims 7, 22, and 33 of the '556 Patent recites: "The vaccine of claim 1, wherein the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium comprises the cytolysin " and "The method of claim 30, wherein the bacterium comprises the cytolysin ", respectively.

Claims 7, 22 and 33 of the '556 Patent	Schmidt reference
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

70. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference and the Schmidt reference in view of US'538 Patent

Claims 7, 22, and 33 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Schmidt reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 7, 22, and 33 is found in the Gentschev reference. Claims 7, 22, and 33 of the '556 Patent recites: "The vaccine of claim 1, wherein the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium comprises the cytolysin " and "The method of claim 30, wherein the bacterium comprises the cytolysin ", respectively.

Claims 7, 22 and 33 of the '556 Patent	Schmidt reference
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

71. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference and the Schmidt reference in view of the Hess reference and the Bielecki reference

Claims 7, 22, and 33 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Schmidt reference in view of the Hess reference and the Bielecki reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

As shown in the chart below, the element and limitation of claims 7, 22, and 33 is found in the Gentschev reference. Claims 7, 22, and 33 of the '556 Patent recites: "The vaccine of claim 1, wherein the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium comprises the cytolysin " and "The method of claim 30, wherein the bacterium comprises the cytolysin ", respectively.

Claims 7, 22 and 33 of the '556 Patent	Schmidt reference
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

72. A substantial new question of patentability as to claims 7 and 22 is raised by the Gentschev reference and the Schmidt reference in view of the Hess reference

Claims 7 and 22 of the '556 Patent are dependent on claims 1 and 16 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Schmidt reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claim 1 and 16 are anticipated under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

As shown in the chart below, the element and limitation of claims 7 and 22 is found in the Gentschev reference. Claims 7 and 22 of the '556 Patent recites: "The vaccine of claim 1, wherein the bacterium comprises the cytolysin" and "The composition of claim 16, wherein the bacterium comprises the cytolysin", respectively.

Claims 7 and 22 of the '556 Patent	Schmidt reference
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

73. A substantial new question of patentability as to claim 33 is raised by the Gentschev reference and the Schmidt reference in view of the Dietrich reference

Claim 33 of the '556 Patent are dependent on claim 30, and is obvious under 35 U.S.C.103, over the Gentschev reference and the Schmidt reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is anticipated under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 33 is found in the Gentschev reference. Claim 33 of the '556 Patent recites: "The method of claim 30, wherein the bacterium comprises the cytolysin ".

Claim 33 of the '556 Patent	Schmidt reference
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

74. A substantial new question of patentability as to claims 7, 22, and 33 is raised by the Gentschev reference and the Schmidt reference in view of the Schmidt reference

Claims 7, 22, and 33 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Schmidt reference in view of the Schmidt and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 7, 22, and 33 is found in the Gentschev reference. Claims 7, 22, and 33 of the '556 Patent recites: "The vaccine of claim 1, wherein the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium comprises the cytolysin " and "The method of claim 30, wherein the bacterium comprises the cytolysin ", respectively.

Claims 7, 22 and 33 of the '556 Patent	Schmidt reference
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

75. A substantial new question of patentability as to claims 8, 23, and 34 is raised by the Gentschev reference

Claims 8, 23, and 34 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are anticipated under 35 U.S.C.102 (b), over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 8, 23, and 34 is found in the Gentschev reference. Claims 8, 23, and 34 of the '556 Patent recite: "The vaccine of claim 1, wherein the agent is synthesized by the bacterium", "The composition of claim 16, wherein the agent is synthesized by the bacterium" and "The method of claim 30, wherein the agent is synthesized by the bacterium", respectively.

Claims 8, 23, and 34 of the '556 Patent	Gentschev reference
"wherein the agent is synthesized by the bacterium "	**Gentschev** provides that the foreign agents, protein products of the genes hlyC, hlyB and hlyD, were synthesized by the bacterium (first paragraph, section 2.2, page 135).

76. A substantial new question of patentability as to claims 8, 23, and 34 is raised by the Gentschev reference

Claims 8, 23, and 34 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 8, 23, and 34 is found in the Gentschev reference. Claims 8, 23, and 34 of the '556 Patent recite: "The vaccine of claim 1, wherein the agent is synthesized by the bacterium", "The composition of claim 16, wherein the agent is synthesized by the bacterium" and "The method of claim 30, wherein the agent is synthesized by the bacterium", respectively.

Claims 8, 23, and 34 of the '556 Patent	Gentschev reference
"wherein the agent is synthesized by the bacterium "	**Gentschev** provides that the foreign agents, protein products of the genes hlyC, hlyB and hlyD, were synthesized by the bacterium (first paragraph, section 2.2, page 135).

77. A substantial new question of patentability as to claims 8 and 23 is raised by the Gentschev reference in view of the Hess reference

Claims 8 and 23 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 8, 23, and 34 is found in the Gentschev reference. Claims 8 and 23 of the '556 Patent recite: "The vaccine of claim 1, wherein the agent is synthesized by the bacterium" and "The method of claim 30, wherein the agent is synthesized by the bacterium", respectively.

Claims 8 and 23 of the '556 Patent	Gentschev reference
"wherein the agent is synthesized by the bacterium "	**Gentschev** provides that the foreign agents, protein products of the genes hlyC, hlyB and hlyD, were synthesized by the bacterium (first paragraph, section 2.2, page 135).

78. A substantial new question of patentability as to claims 8, 23, and 34 is raised by the Gentschev reference in view of the US'538 Patent

Claims 8, 23, and 34 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 8, 23, and 34 is found in the Gentschev reference. Claims 8, 23, and 34 of the '556 Patent recite: "The vaccine of claim 1, wherein the agent is synthesized by the bacterium", "The composition of claim 16,

wherein the agent is synthesized by the bacterium" and "The method of claim 30, wherein the agent is synthesized by the bacterium", respectively.

Claims 8, 23, and 34 of the '556 Patent	Gentschev reference
"wherein the agent is synthesized by the bacterium "	**Gentschev** provides that the foreign agents, protein products of the genes hlyC, hlyB and hlyD, were synthesized by the bacterium (first paragraph, section 2.2, page 135).

79. A substantial new question of patentability as to claims 8, 23, and 34 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference

Claims 8, 23, and 34 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 8, 23, and 34 is found in the Gentschev reference. Claims 8, 23, and 34 of the '556 Patent recite: "The vaccine of claim 1, wherein the agent is synthesized by the bacterium", "The composition of claim 16, wherein the agent is synthesized by the bacterium" and "The method of claim 30, wherein the agent is synthesized by the bacterium", respectively.

Claims 8, 23, and 34 of the '556 Patent	Gentschev reference
"wherein the agent is synthesized by the bacterium "	**Gentschev** provides that the foreign agents, protein products of the genes hlyC, hlyB and hlyD, were synthesized by the bacterium (first paragraph, section 2.2, page 135).

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

80. A substantial new question of patentability as to claims 8, 23, and 34 is raised by the Gentschev reference in view of the Schmidt reference

Claims 8, 23, and 34 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 8, 23, and 34 is found in the Gentschev reference. Claims 8, 23, and 34 of the '556 Patent recite: "The vaccine of claim 1, wherein the agent is synthesized by the bacterium", "The composition of claim 16, wherein the agent is synthesized by the bacterium" and "The method of claim 30, wherein the agent is synthesized by the bacterium", respectively.

Claims 8, 23, and 34 of the '556 Patent	Gentschev reference
"wherein the agent is synthesized by the bacterium "	**Gentschev** provides that the foreign agents, protein products of the genes hlyC, hlyB and hlyD, were synthesized by the bacterium (first paragraph, section 2.2, page 135).

81. A substantial new question of patentability as to claim 34 is raised by the Gentschev reference in view of the Dietrich reference

Claim 34 of the '556 Patent is dependent on claim 30, and is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference and are thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 34 is found in the Gentschev reference. Claim 34 of the '556 Patent recites: "The method of claim 30, wherein the agent is synthesized by the bacterium".

Claims 8, 23, and 34 of the '556 Patent	Gentschev reference
"wherein the agent is synthesized by the bacterium "	**Gentschev** provides that the foreign agents, protein products of the genes hlyC, hlyB and hlyD, were synthesized by the bacterium (first paragraph, section 2.2, page 135).

82. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference

Claims 9 and 35 of the '556 Patent are dependent on claims 1 and 30, respectively, and are anticipated under 35 U.S.C.102 (b), over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 9 and 35 is found in the Gentschev reference. Claims 9 and 35 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 9 and 35 of the '556 Patent	Gentschev reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

83. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference

Claims 9 and 35 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 9 and 35 is found in the Gentschev reference. Claims 9 and 35 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 9 and 35 of the '556 Patent	Gentschev reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

84. A substantial new question of patentability as to claim 9 is raised by the Gentschev reference in view of the Hess reference

Claim 9 of the '556 Patent is dependent on claims 1 and is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claim 1 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claim 9 is found in the Gentschev reference. Claim 9 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins".

Claims 9 of the '556 Patent	Gentschev reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

85. A substantial new question of patentability as to claim 35 is raised by the Gentschev reference in view of the Dietrich reference

Claim 35 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 35 is found in the Gentschev reference. Claim 35 of the '556 Patent recite: "The method of claim 30, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins".

Claim 35 of the '556 Patent	Gentschev reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

86. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference in view of the US'538 Patent

Claims 9 and 35 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 9 and 35 is found in the Gentschev reference. Claims 9 and 35 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 9 and 35 of the '556 Patent	Gentschev reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section

Claims 9 and 35 of the '556 Patent	Gentschev reference
	2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

87. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference

Claims 9 and 35 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 9 and 35 is found in the Gentschev reference. Claims 9 and 35 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 9 and 35 of the '556 Patent	Gentschev reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

88. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference in view of the Schmidt reference

Claims 9 and 35 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 9 and 35 is found in the Gentschev reference. Claims 9 and 35 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 9 and 35 of the '556 Patent	Gentschev reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

89. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference and the Dietrich reference

Claims 9 and 35 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 9 and 35 is found in the Dietrich reference. Claims 9 and 35 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 9 and 35 of the '556 Patent	Dietrich reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Dietrich** discloses bacterial delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to a person skilled in the art at the time of filing of the '556 Patent to combine the disclosures of Dietrich and Gentschev, to utilize the bacteria disclosed in Gentschev as a vehicle for delivering antigenic polypeptides to APC.

90. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference and the Dietrich reference

Claims 9 and 35 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 9 and 35 is found in the Dietrich reference. Claims 9 and 35 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of

claim 30, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC

Claims 9 and 35 of the '556 Patent	Dietrich reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Dietrich** discloses bacterial delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to a person skilled in the art at the time of filing of the '556 Patent to combine the disclosures of Dietrich and Gentschev, to utilize the bacteria disclosed in Gentschev as a vehicle for delivering antigenic polypeptides to APC.

91. A substantial new question of patentability as to claim 9 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference

Claim 9 of the '556 Patent is dependent on claims 1 and is obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claim 1 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claim 9 is found in the Dietrich reference. Claim 9 of the '556 Patent recites: "The vaccine of claim 1, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins".

Claim 9 of the '556 Patent	Dietrich reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Dietrich** discloses bacterial delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to a person skilled in the art at the time of filing of the '556 Patent to combine the disclosures of Dietrich, Hess, and Gentschev, to utilize the bacteria disclosed in Gentschev as a vehicle for delivering antigenic polypeptides to APC.

92. A substantial new question of patentability as to claim 35 is raised by the Gentschev reference and the Dietrich reference in view of the Dietrich reference

Claim 35 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 35 is found in the Dietrich reference. Claim 35 of the '556 Patent recites: "The method of claim 30, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins".

Claim 35 of the '556 Patent	Dietrich reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Dietrich** discloses bacterial delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to a person skilled in the art at the time of filing of the '556 Patent to combine the disclosures of Dietrich and Gentschev, to utilize the bacteria disclosed in Gentschev as a vehicle for delivering antigenic polypeptides to APC.

93. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference and the Dietrich reference in view of the US'538 Patent

Claims 9 and 35 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 9 and 35 is found in the Dietrich reference. Claims 9 and 35 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 9 and 35 of the '556 Patent	Dietrich reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Dietrich** discloses bacterial delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to a person skilled in the art at the time of filing of the '556 Patent to combine the disclosures of Dietrich, US'538 Patent, and Gentschev, to utilize the bacteria disclosed in Gentschev as a vehicle for delivering antigenic polypeptides to APC.

94. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference

Claims 9 and 35 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 9 and 35 is found in the Dietrich reference. Claims 9 and 35 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 9 and 35 of the '556 Patent	Dietrich reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Dietrich** discloses bacterial delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to a person skilled in the art at the time of filing of the '556 Patent to combine the disclosures of Dietrich, Bielecki, Hess, and Gentschev, to utilize the bacteria disclosed in Gentschev as a vehicle for delivering antigenic polypeptides to APC.

95. A substantial new question of patentability as to claims 9 and 35 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference

Claims 9 and 35 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 9 and 35 is found in the Dietrich reference. Claims 9 and 35 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 9 and 35 of the '556 Patent	Dietrich reference
"the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins "	**Dietrich** discloses bacterial delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to a person skilled in the art at the time of filing of the '556 Patent to combine the disclosures of Dietrich, Schmidt, and Gentschev, to utilize the bacteria disclosed in Gentschev as a vehicle for delivering antigenic polypeptides to APC.

96. A substantial new question of patentability as to claims 10, 24, and 36 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference

Claims 10, 24, and 36 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C. 103, over the '556 patent as admitted prior and the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1, 16 and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the patentees of the '556 Patent admitted that the element and limitation of claims 10, 24, and 36 was well known in the art at the time of filing of the '556 Patent. Claims 10, 24, and 36 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome", "The composition of claim 16, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome" and "The method of claim 30, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome", respectively.

Claims 10, 24, and 36 of the '556 Patent	**The '556 Patent**
"bacterium is nonreplicative and nonintegrative into the host cell genome"	**The '556** Patent provides that nonreplicative and nonintegrative bacteria were well known in the art (column 4, lines 33-38).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosure of Gentschev with the admitted prior art disclosure of the '556 Patent, to obtain a nonreplicative bacterium engineered to deliver a gene encoding a foreign agent, according to the method of Gentschev.

97. A substantial new question of patentability as to claims 10, 24, and 36 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference

Claims 10, 24, and 36 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C. 103, over the '556 patent as admitted prior and the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1, 16 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the patentees of the '556 Patent admitted that the element and limitation of claims 10, 24, and 36 was well known in the art at the time of filing of the '556 Patent. Claims 10, 24, and 36 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome", "The composition of claim 16, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome" and "The method of claim 30, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome", respectively.

Claims 10, 24, and 36 of the '556 Patent	**The '556 Patent**
"bacterium is nonreplicative and nonintegrative into the host cell genome"	**The '556** Patent provides that nonreplicative and nonintegrative bacteria were well known in the art (column 4, lines 33-38).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosure of Gentschev with the admitted prior art disclosure of the '556 Patent, to obtain a nonreplicative bacterium engineered to deliver a gene encoding a foreign agent, according to the method of Gentschev.

98. A substantial new question of patentability as to claims 10, 24, and 36 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of US'538 Patent

Claims 10, 24, and 36 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C. 103, over the '556 patent as admitted prior and the Gentschev reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1, 16 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the patentees of the '556 Patent admitted that the element and limitation of claims 10, 24, and 36 was well known in the art at the time of filing of the '556 Patent. Claims 10, 24, and 36 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome", "The composition of claim 16, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome" and "The method of claim 30, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome", respectively.

Claims 10, 24, and 36 of the '556 Patent	**The '556 Patent**
"bacterium is nonreplicative and nonintegrative into the host cell genome"	**The '556** Patent provides that nonreplicative and nonintegrative bacteria were well known in the art (column 4, lines 33-38).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosure of Gentschev and US'538 Patent with the admitted prior art disclosure of the '556 Patent, to obtain a nonreplicative bacterium engineered to deliver a gene encoding a foreign agent, according to the method of Gentschev.

99. A substantial new question of patentability as to claims 10, 24, and 36 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Hess reference and the Bielecki reference

Claims 10, 24, and 36 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C. 103, over the '556 patent as admitted prior and the Gentschev reference in view of the Hess reference and the Bielecki reference and are thus unpatentable.

As shown hereinabove, claims 1, 16 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

As shown in the chart below, the patentees of the '556 Patent admitted that the element and limitation of claims 10, 24, and 36 was well known in the art at the time of filing of the '556 Patent. Claims 10, 24, and 36 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome", "The composition of claim 16, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome" and "The method of claim 30, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome", respectively.

Claims 10, 24, and 36 of the '556 Patent	**The '556 Patent**
"bacterium is nonreplicative and nonintegrative into the host cell genome"	**The '556** Patent provides that nonreplicative and nonintegrative bacteria were well known in the art (column 4, lines 33-38).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosure of Gentschev, Hess, and Bielecki with the admitted prior art disclosure of the '556 Patent, to obtain a nonreplicative bacterium engineered to deliver a gene encoding a foreign agent, according to the method of Gentschev.

100. A substantial new question of patentability as to claims 10 and 24 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Hess reference

Claims 10 and 24 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C. 103, over the '556 patent as admitted prior and the Gentschev reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the patentees of the '556 Patent admitted that the element and limitation of claims 10 and 24 was well known in the art at the time of filing of the '556 Patent. Claims 10 and 24 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome" and "The composition of claim 16, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome", respectively.

Claims 10, 24, and 36 of the '556 Patent	**The '556 Patent**
"bacterium is nonreplicative and nonintegrative into the host cell genome"	**The '556** Patent provides that nonreplicative and nonintegrative bacteria were well known in the art (column 4, lines 33-38).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosure of Gentschev and Hess with the admitted prior art disclosure of the '556 Patent, to obtain a nonreplicative bacterium engineered to deliver a gene encoding a foreign agent, according to the method of Gentschev.

101. A substantial new question of patentability as to claim 36 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Dietrich reference

Claim 36 of the '556 Patent are dependent on claim 30 and is obvious under 35 U.S.C. 103, over the '556 patent as admitted prior and the Gentschev reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the patentees of the '556 Patent admitted that the element and limitation of claims 10 and 24 was well known in the art at the time of filing of the '556 Patent. Claims 10 and 24 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome" and "The composition of claim 16, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome", respectively.

Claims 10, 24, and 36 of the '556 Patent	**The '556 Patent**
"bacterium is nonreplicative and nonintegrative into the host cell genome"	**The '556** Patent provides that nonreplicative and nonintegrative bacteria were well known in the art (column 4, lines 33-38).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosure of Gentschev and Dietrich with the admitted prior art disclosure of the '556 Patent, to obtain a nonreplicative bacterium engineered to deliver a gene encoding a foreign agent, according to the method of Gentschev.

102. A substantial new question of patentability as to claims 10, 24, and 36 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Schmidt reference

Claims 10, 24, and 36 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C. 103, over the '556 patent as admitted prior and the Gentschev reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the patentees of the '556 Patent admitted that the element and limitation of claims 10, 24, and 36 was well known in the art at the time of filing of the '556 Patent. Claims 10, 24, and 36 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome", "The composition of claim 16, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome" and "The method of claim 30, wherein the bacterium is nonreplicative and nonintegrative into the host cell genome", respectively.

Claims 10, 24, and 36 of the '556 Patent	**The '556 Patent**
"bacterium is nonreplicative and nonintegrative into the host cell genome"	**The '556** Patent provides that nonreplicative and nonintegrative bacteria were well known in the art (column 4, lines 33-38).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosure of Gentschev and Schmidt with the admitted prior art disclosure of the '556 Patent, to obtain a nonreplicative bacterium engineered to deliver a gene encoding a foreign agent, according to the method of Gentschev.

103. A substantial new question of patentability as to claims 11, 25, and 37 is raised by the Gentschev reference and the Dietrich reference

Claims 11, 25, and 37 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 11, 25, and 37 is found in the Dietrich reference and in the Gentschev reference. Claims 11, 25, and 37 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli", "The composition of claim 16, wherein he bacterium is dead or non-viable laboratory strain of E. coli", and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli", respectively.

Claims 11, 25, and 37 of the '556 Patent	**Prior Art reference**
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain, which is a laboratory strain (Table 1, page 136).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Gentschev and Dietrich, to obtain a dead or non-viable E. coli bacterium, according to the method of Gentschev.

104. A substantial new question of patentability as to claims 11, 25, and 37 is raised by the Gentschev reference and the Dietrich reference

Claims 11, 25, and 37 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 11, 25, and 37 is found in the Dietrich reference and in the Gentschev reference. Claims 11, 25, and 37 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli", "The composition of claim 16, wherein he bacterium is dead or non-viable laboratory strain of E. coli", and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli", respectively.

Claims 11, 25, and 37 of the '556 Patent	**Prior Art reference**
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain, which is a laboratory strain (Table 1, page 136).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Gentschev and Dietrich, to obtain a dead or non-viable E. coli bacterium, according to the method of Gentschev.

105. A substantial new question of patentability as to claims 11 and 25 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference

Claims 11 and 25 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 11 and 25 is found in the Dietrich reference and in the Gentschev reference. Claims 11 and 25 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli" and "The composition of claim 16, wherein he bacterium is dead or non-viable laboratory strain of E. coli", respectively.

Claims 11 and 25 of the '556 Patent	Prior Art reference
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain, which is a laboratory strain (Table 1, page 136).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Gentschev, Hess, and Dietrich, to obtain a dead or non-viable E. coli bacterium, according to the method of Gentschev.

106. A substantial new question of patentability as to claims 11, 25, and 37 is raised by the Gentschev reference and the Dietrich reference in view of the US'538 Patent

Claims 11, 25, and 37 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 11, 25, and 37 is found in the Dietrich reference and in the Gentschev reference. Claims 11, 25, and 37 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli", "The composition of claim 16, wherein he bacterium is dead or non-viable laboratory strain of E. coli", and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli", respectively.

Claims 11, 25, and 37 of the '556 Patent	**Prior Art reference**
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain, which is a laboratory strain (Table 1, page 136).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Gentschev, US'538 Patent, and Dietrich, to obtain a dead or non-viable E. coli bacterium, according to the method of Gentschev.

107. A substantial new question of patentability as to claims 11, 25, and 37 is raised by the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference

Claims 11, 25, and 37 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 11, 25, and 37 is found in the Dietrich reference and in the Gentschev reference. Claims 11, 25, and 37 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli", "The composition of claim 16, wherein he bacterium is dead or non-viable laboratory strain of E. coli", and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli", respectively.

Claims 11, 25, and 37 of the '556 Patent	**Prior Art reference**
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain, which is a laboratory strain (Table 1, page 136).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Gentschev, Bielecki, Hess, and Dietrich, to obtain a dead or non-viable E. coli bacterium, according to the method of Gentschev.

108. A substantial new question of patentability as to claims 11, 25, and 37 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference

Claims 11, 25, and 37 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 11, 25, and 37 is found in the Dietrich reference and in the Gentschev reference. Claims 11, 25, and 37 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli", "The composition of claim 16, wherein he bacterium is dead or non-viable laboratory strain of E. coli", and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli", respectively.

Claims 11, 25, and 37 of the '556 Patent	**Prior Art reference**
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain, which is a laboratory strain (Table 1, page 136).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Gentschev, Schmidt, and Dietrich, to obtain a dead or non-viable E. coli bacterium, according to the method of Gentschev.

109. A substantial new question of patentability as to claim 37 is raised by the Gentschev reference in view of the Dietrich reference

Claim 37 of the '556 Patent is dependent on claim 30, and is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 37 is found in the Dietrich reference and in the Gentschev reference. Claim 37 of the '556 Patent recites: "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli".

Claim 37 of the '556 Patent	Prior Art reference
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain, which is a laboratory strain (Table 1, page 136).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosures of Gentschev and Dietrich, to obtain a dead or non-viable E. coli bacterium, according to the method of Gentschev.

110. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference

Claims 12, 26, and 38 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are anticipated under 35 U.S.C.102 (b), over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 12, 26, and 38 is found in the Gentschev reference. Claims 12, 26, and 38 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 12, 26, and 38 of the '556 Patent	Gentschev reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

111. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference

Claims 12, 26, and 38 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 12, 26, and 38 is found in the Gentschev reference. Claims 12, 26, and 38 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 12, 26, and 38 of the '556 Patent	Gentschev reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

112. A substantial new question of patentability as to claims 12 and 26 is raised by the Gentschev reference in view of the Hess reference

Claims 12 and 26 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 12, 26, and 38 is found in the Gentschev reference. Claims 12 and 26 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 12, 26, and 38 of the '556 Patent	Gentschev reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

113. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference in view of the US'538 Patent

Claims 12, 26, and 38 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 12, 26, and 38 is found in the Gentschev reference. Claims 12, 26, and 38 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 12, 26, and 38 of the '556 Patent	**Gentschev reference**
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

114. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference

Claims 12, 26, and 38 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 12, 26, and 38 is found in the Gentschev reference. Claims 12, 26, and 38 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 12, 26, and 38 of the '556 Patent	**Gentschev reference**
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

115. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference in view of the Schmidt reference

Claims 12, 26, and 38 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 12, 26, and 38 is found in the Gentschev reference. Claims 12, 26, and 38 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is a

laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 12, 26, and 38 of the '556 Patent	Gentschev reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

116. A substantial new question of patentability as to claim 38 is raised by the Gentschev reference in view of the Dietrich reference

Claim 38 of the '556 Patent is dependent on claim 30, and is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claims 12, 26, and 38 is found in the Gentschev reference. Claim 38 of the '556 Patent recites: "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin".

Claims 12, 26, and 38 of the '556 Patent	Gentschev reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

117. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference and the Schmidt reference

Claims 12, 26, and 38 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 12, 26, and 38 is found in the Schmidt reference, and in the Gentschev reference. Claims 12, 26, and 38 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 12, 26, and 38 of the '556 Patent	Prior Art reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Schmidt disclosure providing a hemolysin (cytolysin)-positive strain with Gentschev's laboratory strain of E. coli.

118. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference and the Schmidt reference

Claims 12, 26, and 38 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 12, 26, and 38 is found in the Schmidt reference, and in the Gentschev reference. Claims 12, 26, and 38 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 12, 26, and 38 of the '556 Patent	**Prior Art reference**
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Schmidt disclosure providing a hemolysin (cytolysin)-positive strain with Gentschev's laboratory strain of E. coli.

119. A substantial new question of patentability as to claims 12 and 26 is raised by the Gentschev reference and the Schmidt reference in view of the Hess reference

Claims 12 and 26 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Schmidt reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 12 and 26 is found in the Schmidt reference, and in the Gentschev reference. Claims 12 and 26 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin"and "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 12 and 26 of the '556 Patent	Prior Art reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Schmidt disclosure providing a hemolysin (cytolysin)-positive strain with Gentschev's laboratory strain of E. coli.

120. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference and the Schmidt reference in view of the US'538 Patent

Claims 12, 26, and 38 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Schmidt reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 12, 26, and 38 is found in the Schmidt reference, and in the Gentschev reference. Claims 12, 26, and 38 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 12, 26, and 38 of the '556 Patent	**Prior Art reference**
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Schmidt disclosure providing a hemolysin (cytolysin)-positive strain with Gentschev's laboratory strain of E. coli.

121. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference and the Schmidt reference in view of the Bielecki reference and the Hess reference

Claims 12, 26, and 38 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Schmidt reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 12, 26, and 38 is found in the Schmidt reference, and in the Gentschev reference. Claims 12, 26, and 38 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 12, 26, and 38 of the '556 Patent	**Prior Art reference**
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Schmidt disclosure providing a hemolysin (cytolysin)-positive strain with Gentschev's laboratory strain of E. coli.

122. A substantial new question of patentability as to claims 12, 26, and 38 is raised by the Gentschev reference and the Schmidt reference in view of the Schmidt reference

Claims 12, 26, and 38 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Schmidt reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 12, 26, and 38 is found in the Schmidt reference, and in the Gentschev reference. Claims 12, 26, and 38 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 12, 26, and 38 of the '556 Patent	**Prior Art reference**
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Schmidt disclosure providing a hemolysin (cytolysin)-positive strain with Gentschev's laboratory strain of E. coli.

123. A substantial new question of patentability as to claim 38 is raised by the Gentschev reference and the Schmidt reference in view of the Dietrich reference

Claim 38 of the '556 Patent is dependent on claim 30, and is obvious under 35 U.S.C.103, over the Gentschev reference and the Schmidt reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 38 is found in the Schmidt reference, and in the Gentschev reference. Claim 38 of the '556 Patent recites: "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli and the bacterium comprises the cytolysin".

Claim 38 of the '556 Patent	Prior Art reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Schmidt disclosure providing a hemolysin (cytolysin)-positive strain with Gentschev's laboratory strain of E. coli.

124. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich reference

Claims 13, 27, and 39 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 13, 27, and 39 is found in the Dietrich reference, and in the Gentschev reference. Claims 13, 27, and 39 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 13, 27, and 39 of the '556 Patent	**Prior Art reference**
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure. Moreover, one of skill in the art would be motivated to eliminate the bacteria specie for safety and antigen exposure reasons.

125. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich reference

Claims 13, 27, and 39 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 13, 27, and 39 is found in the Dietrich reference, and in the Gentschev reference. Claims 13, 27, and 39 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 13, 27, and 39 of the '556 Patent	**Prior Art reference**
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure. Moreover, one of skill

in the art would be motivated to eliminate the bacteria specie for safety and antigen exposure reasons.

126. A substantial new question of patentability as to claims 13 and 27 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference

Claims 13 and 27 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 13 and 27 is found in the Dietrich reference, and in the Gentschev reference. Claims 13 and 27 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 13 and 27 of the '556 Patent	Prior Art reference
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as

an efficient method to kill the bacteria with the Gentschev disclosure. Moreover, one of skill in the art would be motivated to eliminate the bacteria specie for safety and antigen exposure reasons.

127. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich reference in view of the US'538 Patent

Claims 13, 27, and 39 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 13, 27, and 39 is found in the Dietrich reference, and in the Gentschev reference. Claims 13, 27, and 39 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 13, 27, and 39 of the '556 Patent	Prior Art reference
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure. Moreover, one of skill in the art would be motivated to eliminate the bacteria specie for safety and antigen exposure reasons.

128. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference

Claims 13, 27, and 39 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 13, 27, and 39 is found in the Dietrich reference, and in the Gentschev reference. Claims 13, 27, and 39 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 13, 27, and 39 of the '556 Patent	**Prior Art reference**
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).

Claims 13, 27, and 39 of the '556 Patent	Prior Art reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure. Moreover, one of skill in the art would be motivated to eliminate the bacteria specie for safety and antigen exposure reasons.

129. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference

Claims 13, 27, and 39 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 13, 27, and 39 is found in the Dietrich reference, and in the Gentschev reference. Claims 13, 27, and 39 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is

dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 13, 27, and 39 of the '556 Patent	Prior Art reference
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure. Moreover, one of skill in the art would be motivated to eliminate the bacteria specie for safety and antigen exposure reasons.

130. A substantial new question of patentability as to claim 39 is raised by the Gentschev reference and the Dietrich reference in view of the Dietrich reference

Claim 39 of the '556 Patent is dependent on claim 30, and is obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 39 is found in the Dietrich reference, and in the Gentschev reference. Claim 39 of the '556 Patent recites: "The

method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin".

Claim 39 of the '556 Patent	Prior Art reference
"the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure. Moreover, one of skill in the art would be motivated to eliminate the bacteria specie for safety and antigen exposure reasons.

131. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich reference

Claims 13, 27, and 39 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 13, 27, and 39 is found in the Dietrich reference, in the Schmidt reference, and in the Gentschev reference. Claims 13, 27, and 39 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the

cytolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 13, 27, and 39 of the '556 Patent	Prior Art reference
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a method to kill a bacteria used with the Gentschev disclosure. It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Schmidt disclosure providing a bacteria comprising EHEC hemolysin (cytolysin) - with the Gentschev disclosure.

132. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich reference

Claims 13, 27, and 39 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 13, 27, and 39 is found in the Dietrich reference, in the Schmidt reference, and in the Gentschev reference.

Claims 13, 27, and 39 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 13, 27, and 39 of the '556 Patent	**Prior Art reference**
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a method to kill a bacteria used with the Gentschev disclosure. It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Schmidt disclosure providing a bacteria comprising EHEC hemolysin (cytolysin)- with the Gentschev disclosure.

133. A substantial new question of patentability as to claims 13 and 27 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference

Claims 13 and 27 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 13 and 27 is found in the Dietrich reference, in the Schmidt reference, and in the Gentschev reference. Claims 13 and 27 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 13 and 27 of the '556 Patent	**Prior Art reference**
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a method to kill a bacteria used with the Gentschev disclosure. It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Schmidt disclosure providing a bacteria comprising EHEC hemolysin (cytolysin)- with the Gentschev disclosure.

134. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich reference in view of the US'538 Patent

Claims 13, 27, and 39 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 13, 27, and 39 is found in the Dietrich reference, in the Schmidt reference, and in the Gentschev reference. Claims 13, 27, and 39 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 13, 27, and 39 of the '556 Patent	**Prior Art reference**
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a method to kill a bacteria used with the Gentschev disclosure. It would have been obvious to one of skill in the art at the time of filing

of the '556 Patent to combine the Schmidt disclosure providing a bacteria comprising EHEC hemolysin (cytolysin) - with the Gentschev disclosure.

135. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference

Claims 13, 27, and 39 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 13, 27, and 39 is found in the Dietrich reference, in the Schmidt reference, and in the Gentschev reference. Claims 13, 27, and 39 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 13, 27, and 39 of the '556 Patent	**Prior Art reference**
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a method to kill a bacteria used with the Gentschev disclosure. It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Schmidt disclosure providing a bacteria comprising EHEC hemolysin (cytolysin)- with the Gentschev disclosure.

136. A substantial new question of patentability as to claims 13, 27, and 39 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference

Claims 13, 27, and 39 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 13, 27, and 39 is found in the Dietrich reference, in the Schmidt reference, and in the Gentschev reference. Claims 13, 27, and 39 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin", respectively.

Claims 13, 27, and 39 of the '556 Patent	**Prior Art reference**
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli

Claims 13, 27, and 39 of the '556 Patent	Prior Art reference
	5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a method to kill a bacteria used with the Gentschev disclosure. It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Schmidt disclosure providing a bacteria comprising EHEC hemolysin (cytolysin) - with the Gentschev disclosure.

137. A substantial new question of patentability as to claim 39 is raised by the Gentschev reference and the Dietrich reference and the Schmidt reference in view of the Dietrich reference

Claim 39 of the '556 Patent is dependent on claim 30, and is obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 39 is found in the Dietrich reference, in the Schmidt reference, and in the Gentschev reference. Claim 39 of the '556 Patent recite: "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin".

Claim 39 of the '556 Patent	Prior Art reference
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory

Claim 39 of the '556 Patent	Prior Art reference
	strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a method to kill a bacteria used with the Gentschev disclosure. It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Schmidt disclosure providing a bacteria comprising EHEC hemolysin (cytolysin) - with the Gentschev disclosure.

138. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference and the Dietrich reference

Claims 14, 28, and 40 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 14, 28, and 40 is found in the Dietrich reference and in the Gentschev reference. 14, 28, and 40 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", respectively.

Claims 14, 28, and 40 of the '556 Patent	Prior Art reference
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).
"the cytolysin is listeriolysin"	**Gentschev** discloses expression of LLO in a recombinant Salmonella strain (first paragraph, section 2.3, page 136).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli comprising listeriolysin .

139. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference and the Dietrich reference

Claims 14, 28, and 40 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 14, 28, and 40 is found in the Dietrich reference and in the Gentschev reference. 14, 28, and 40 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin" and

"The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", respectively.

Claims 14, 28, and 40 of the '556 Patent	Prior Art reference
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).
"the cytolysin is listeriolysin"	**Gentschev** discloses expression of LLO in a recombinant Salmonella strain (first paragraph, section 2.3, page 136).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli comprising listeriolysin .

140. A substantial new question of patentability as to claims 14 and 28 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference

Claims 14 and 28 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 14 and 28 is found in the Dietrich reference and in the Gentschev reference. Claims 14 and 28 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain

of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin"and "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", respectively.

Claims 14, 28, and 40 of the '556 Patent	Prior Art reference
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).
"the cytolysin is listeriolysin"	**Gentschev** discloses expression of LLO in a recombinant Salmonella strain (first paragraph, section 2.3, page 136).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli comprising listeriolysin .

141. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference and the Dietrich reference in view of the US'538 Patent

Claims 14, 28, and 40 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 14, 28, and 40 is found in the Dietrich reference and in the Gentschev reference. Claims 14, 28, and 40 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", respectively.

Claims 14, 28, and 40 of the '556 Patent	**Prior Art reference**
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).
"the cytolysin is listeriolysin"	**Gentschev** discloses expression of LLO in a recombinant Salmonella strain (first paragraph, section 2.3, page 136).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli comprising listeriolysin .

142. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference

Claims 14, 28, and 40 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 14, 28, and 40 is found in the Dietrich reference and in the Gentschev reference. Claims 14, 28, and 40 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", respectively.

Claims 14, 28, and 40 of the '556 Patent	**Prior Art reference**
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).
"the cytolysin is listeriolysin"	**Gentschev** discloses expression of LLO in a recombinant Salmonella strain (first paragraph, section 2.3, page 136).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli comprising listeriolysin .

143. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference

Claims 14, 28, and 40 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 14, 28, and 40 is found in the Dietrich reference and in the Gentschev reference. Claims 14, 28, and 40 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", respectively.

Claims 14, 28, and 40 of the '556 Patent	**Prior Art reference**
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli

Claims 14, 28, and 40 of the '556 Patent	Prior Art reference
	5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).
"the cytolysin is listeriolysin"	**Gentschev** discloses expression of LLO in a recombinant Salmonella strain (first paragraph, section 2.3, page 136).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli comprising listeriolysin .

144. A substantial new question of patentability as to claim 40 is raised by the Gentschev reference and the Dietrich reference in view of the Dietrich reference

Claim 40 of the '556 Patent is dependent on claim 30, and is obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 40 is found in the Dietrich reference and in the Gentschev reference. Claim 40 of the '556 Patent recites: "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin".

Claims 14, 28, and 40 of the '556 Patent	Prior Art reference
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).

Claims 14, 28, and 40 of the '556 Patent	Prior Art reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Gentschev's** bacterium comprises hly gene (cytolysin) of L. monocytogenes which is LLO (first paragraph, section 2.4, page 137).
"the cytolysin is listeriolysin"	**Gentschev** discloses expression of LLO in a recombinant Salmonella strain (first paragraph, section 2.3, page 136).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli comprising listeriolysin .

145. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference

Claims 14, 28, and 40 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 14, 28, and 40 is found in the Dietrich reference, in the Bielecki reference, in the Schmidt reference, and in the Gentschev reference. 14, 28, and 40 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium

comprises the cytolysin and the cytolysin is listeriolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", respectively.

Claims 14, 28, and 40 of the '556 Patent	Prior Art reference
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).
"the cytolysin is listeriolysin"	**Bielecki** describes production of LLO by a heterologous bacterial species (page 175, second column, first paragraph).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli, with the Schmidt disclosure providing cytolysin, and with the Bielecki disclosure providing listeriolysin.

146. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference

Claims 14, 28, and 40 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 14, 28, and 40 is found in the Dietrich reference, in the Bielecki reference, in the Schmidt reference, and in the

Gentschev reference. 14, 28, and 40 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", respectively.

Claims 14, 28, and 40 of the '556 Patent	Prior Art reference
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).
"the cytolysin is listeriolysin"	**Bielecki** describes production of LLO by a heterologous bacterial species (page 175, second column, first paragraph).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli, with the Schmidt disclosure providing cytolysin, and with the Bielecki disclosure providing listeriolysin.

147. A substantial new question of patentability as to claims 14 and 28 is raised by the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the Hess reference

Claims 14 and 28 of the '556 Patent are dependent on claims 1 and 16, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference, the Dietrich reference, the

Bielecki reference, and the Schmidt reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 16 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 14 and 28 is found in the Dietrich reference, in the Bielecki reference, in the Schmidt reference, and in the Gentschev reference. 14 and 28 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin" and "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", respectively.

Claims 14 and 28 of the '556 Patent	**Prior Art reference**
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).
"the cytolysin is listeriolysin"	**Bielecki** describes production of LLO by a heterologous bacterial species (page 175, second column, first paragraph).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli, with the Schmidt disclosure providing cytolysin, and with the Bielecki disclosure providing listeriolysin.

148. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the US'538 Patent

Claims 14, 28, and 40 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 14, 28, and 40 is found in the Dietrich reference, in the Bielecki reference, in the Schmidt reference, and in the Gentschev reference. 14, 28, and 40 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", respectively.

Claims 14, 28, and 40 of the '556 Patent	**Prior Art reference**
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).
"the cytolysin is listeriolysin"	**Bielecki** describes production of LLO by a heterologous bacterial species (page 175, second column, first paragraph).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli, with the Schmidt disclosure providing cytolysin, and with the Bielecki disclosure providing listeriolysin.

149. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the Bielecki reference and the Hess reference

Claims 14, 28, and 40 of the '556 Patent are dependent on claims 1, 16, and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 14, 28, and 40 is found in the Dietrich reference, in the Bielecki reference, in the Schmidt reference, and in the Gentschev reference. 14, 28, and 40 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", respectively.

Claims 14, 28, and 40 of the '556 Patent	Prior Art reference
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).
"the cytolysin is listeriolysin"	**Bielecki** describes production of LLO by a heterologous bacterial species (page 175, second column, first paragraph).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli, with the Schmidt disclosure providing cytolysin, and with the Bielecki disclosure providing listeriolysin.

150. A substantial new question of patentability as to claims 14, 28, and 40 is raised by the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the Schmidt reference

Claims 14, 28, and 40 of the '556 Patent are dependent on claims 1, 16, and 30 respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1, 16, and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 14, 28, and 40 is found in the Dietrich reference, in the Bielecki reference, in the Schmidt reference, and in the Gentschev reference. 14, 28, and 40 of the '556 Patent recite: "The vaccine of claim 1,

wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", "The composition of claim 16, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin" and "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin", respectively.

Claims 14, 28, and 40 of the '556 Patent	**Prior Art reference**
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).
"the cytolysin is listeriolysin"	**Bielecki** describes production of LLO by a heterologous bacterial species (page 175, second column, first paragraph).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli, with the Schmidt disclosure providing cytolysin, and with the Bielecki disclosure providing listeriolysin.

151. A substantial new question of patentability as to claim 40 is raised by the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the Dietrich reference

Claim 40 of the '556 Patent is dependent on claim 30, and is obvious under 35 U.S.C.103, over the Gentschev reference, the Dietrich reference, the Bielecki reference, and the Schmidt reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 40 is found in the Dietrich reference, in the Bielecki reference, in the Schmidt reference, and in the Gentschev reference. Claim 40 of the '556 Patent recite: "The method of claim 30, wherein the bacterium is dead or non-viable laboratory strain of E. coli and the bacterium comprises the cytolysin and the cytolysin is listeriolysin".

Claims 14, 28, and 40 of the '556 Patent	**Prior Art reference**
" the bacterium is dead or non-viable"	**Dietrich** discloses the use of a phage lysin-mediated plasmid release as an efficient method to kill the bacteria (first column, page 183).
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"the bacterium comprises the cytolysin"	**Schmidt** discloses EHEC hemolysin (cytolysin)-positive strain EDL933 (laboratory strain) (page 1058).
"the cytolysin is listeriolysin"	**Bielecki** describes production of LLO by a heterologous bacterial species (page 175, second column, first paragraph).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated plasmid release as an efficient method to kill the bacteria with the Gentschev disclosure providing a laboratory strain of E. coli, with the Schmidt disclosure providing cytolysin, and with the Bielecki disclosure providing

152. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference

Claims 15 and 41 of the '556 Patent are dependent on claims 1 and 30, respectively, and are anticipated under 35 U.S.C.102(b), over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 15 and 41 is found in the Gentschev reference. Claims 15 and 41 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 15 and 41 of the '556 Patent	Gentschev reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins"	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

153. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference

Claims 15 and 41 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 15 and 41 is found in the Gentschev reference. Claims 15 and 41 of the '556 Patent recite: "The vaccine of claim

1, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 15 and 41 of the '556 Patent	Gentschev reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins"	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

154. A substantial new question of patentability as to claim 15 is raised by the Gentschev reference in view of the Hess reference

Claim 15 of the '556 Patent is dependent on claims 1 and is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claim 1 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claims 15 and 41 is found in the Gentschev reference. Claim 15 of the '556 Patent recites: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-

presenting cells antigenic polypeptides which are presented in association with MHC proteins".

Claim 15 of the '556 Patent	Gentschev reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins"	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

155. A substantial new question of patentability as to claim 41 is raised by the Gentschev reference in view of the Dietrich reference

Claim 41 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 41 is found in the Gentschev reference. Claim 41 of the '556 Patent recites: "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins".

Claim 41 of the '556 Patent	Gentschev reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory

Claim 41 of the '556 Patent	Gentschev reference
	strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins"	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

156. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference in view of the US'538 Patent

Claims 15 and 41 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 15 and 41 is found in the Gentschev reference. Claims 15 and 41 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 15 and 41 of the '556 Patent	Gentschev reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells

Claims 15 and 41 of the '556 Patent	Gentschev reference
which are presented in association with MHC proteins"	antigenic polypeptides which are presented in association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

157. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference in view of the Bielecki reference and the Hess reference

Claims 15 and 41 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 15 and 41 is found in the Gentschev reference. Claims 15 and 41 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 15 and 41 of the '556 Patent	Gentschev reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in

Claims 15 and 41 of the '556 Patent	Gentschev reference
MHC proteins"	association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

158. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference in view of the Schmidt reference

Claims 15 and 41 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 15 and 41 is found in the Gentschev reference. Claims 15 and 41 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 15 and 41 of the '556 Patent	Gentschev reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins"	**Gentschev** provides that the bacterium is engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins (first paragraph, section 2.1 page 134). **Gentschev** discloses induction of immune

Claims 15 and 41 of the '556 Patent	Gentschev reference
	responses in mice vaccinated with their recombinant bacteria (first paragraph, section 2.4 page 137). Thus, antigenic polypeptides were presented on antigen-presenting cells (APCs) presented in association with MHC proteins.

159. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference and the Dietrich reference

Claims 15 and 41 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 15 and 41 is found in the Dietrich reference and in the Gentschev reference. Claims 15 and 41 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 15 and 41 of the '556 Patent	Prior Art reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins"	**Dietrich** discloses the delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated APC-MHC

antigenic delivery system with the Gentschev disclosure providing a laboratory strain of E. coli.

160. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference and the Dietrich reference

Claims 15 and 41 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claims 15 and 41 is found in the Dietrich reference and in the Gentschev reference. Claims 15 and 41 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 15 and 41 of the '556 Patent	Prior Art reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins"	**Dietrich** discloses the delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated APC-MHC antigenic delivery system with the Gentschev disclosure providing a laboratory strain of E. coli.

161. A substantial new question of patentability as to claim 15 is raised by the Gentschev reference and the Dietrich reference in view of the Hess reference

Claim 15 of the '556 Patent is dependent on claims 1 and is obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Hess reference and are thus unpatentable.

As shown hereinabove, claim 1 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claim 15 is found in the Dietrich reference and in the Gentschev reference. Claim 15 of the '556 Patent recites: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins".

Claims 15 of the '556 Patent	Prior Art reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins"	**Dietrich** discloses the delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated APC-MHC antigenic delivery system with the Gentschev disclosure providing a laboratory strain of E. coli.

162. A substantial new question of patentability as to claim 41 is raised by the Gentschev reference and the Dietrich reference in view of the Dietrich reference

Claim 41 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 41 is found in the Dietrich reference and in the Gentschev reference. Claim 15 and 41 of the '556 Patent recites: "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins".

Claim 41 of the '556 Patent	Prior Art reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins"	**Dietrich** discloses the delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated APC-MHC antigenic delivery system with the Gentschev disclosure providing a laboratory strain of E. coli.

163. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference and the Dietrich reference in view of the US'538 Patent

Claims 15 and 41 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of US'538 Patent and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claims 15 and 41 is found in the Dietrich reference and in the Gentschev reference. Claims 15 and 41 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 15 and 41 of the '556 Patent	Prior Art reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins"	**Dietrich** discloses the delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated APC-MHC antigenic delivery system with the Gentschev disclosure providing a laboratory strain of E. coli.

164. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference

Claims 15 and 41 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Bielecki reference and the Hess reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Bielecki reference and the Hess reference.

As shown in the chart below, the element and limitation of claims 15 and 41 is found in the Dietrich reference and in the Gentschev reference. Claims 15 and 41 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 15 and 41 of the '556 Patent	**Prior Art reference**
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins"	**Dietrich** discloses the delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated APC-MHC antigenic delivery system with the Gentschev disclosure providing a laboratory strain of E. coli.

165. A substantial new question of patentability as to claims 15 and 41 is raised by the Gentschev reference and the Dietrich reference in view of the Schmidt reference

Claims 15 and 41 of the '556 Patent are dependent on claims 1 and 30, respectively, and are obvious under 35 U.S.C.103, over the Gentschev reference and the Dietrich reference in view of the Schmidt reference and are thus unpatentable.

As shown hereinabove, claims 1 and 30 are obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claims 15 and 41 is found in the Dietrich reference and in the Gentschev reference. Claims 15 and 41 of the '556 Patent recite: "The vaccine of claim 1, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins" and "The method of claim 30, wherein the bacterium is a laboratory strain of E. coli engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins", respectively.

Claims 15 and 41 of the '556 Patent	Prior Art reference
"laboratory strain of E. coli"	**Gentschev** discloses the use of E. coli 5K[pANN202-812] strain which is a laboratory strain (Table 1, page 136).
"engineered to deliver to antigen-presenting cells antigenic polypeptides which are presented in association with MHC proteins"	**Dietrich** discloses the delivery of antigenic polypeptides to APC, presented in association with MHC proteins (second full paragraph, page 184).

It would have been obvious to one of skill in the art at the time of filing of the '556 Patent to combine the Dietrich disclosure providing a phage lysin-mediated APC-MHC antigenic delivery system with the Gentschev disclosure providing a laboratory strain of E. coli.

166. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference

Claim 29 of the '556 Patent is dependent on claim 16 and is anticipated under 35 U.S.C.102 (b), over the Gentschev reference and is thus unpatentable.

As shown hereinabove, claim 16 is anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claim 29 is found in the Gentschev reference. Claim 29 of the '556 Patent recites: "The bacterium of claim 1, wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor".

Claim 29 of the '556 Patent	Gentschev reference
"wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor"	**Gentschev** discloses that the hemolysin secretion machinery can be successfully applied to express and secrete various heterologous antigens. Specifically, Gentschev shows that antibiotic, anti-bacterial, antigens provide effective protection of mice against a normally lethal L. Monocytogenes infection after vaccination with attenuated S. typhimurium secreting either LLO or p60. The system developed by Gentschev permits in-frame insertion of a gene or a gene fragments for any given protein antigen and thus includes antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor antigens. (section 3, page 138).

167. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference

Claim 29 of the '556 Patent is dependent on claim 16 and is obvious under 35 U.S.C.103, over the Gentschev reference and is thus unpatentable.

As shown hereinabove, claim 16 is obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claim 29 is found in the Gentschev reference. Claim 29 of the '556 Patent recites: "The bacterium of claim 1, wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor".

Claim 29 of the '556 Patent	Gentschev reference
"wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor"	**Gentschev** discloses that the hemolysin secretion machinery can be successfully applied to express and secrete various heterologous antigens. Specifically, Gentschev shows that antibiotic, anti-bacterial, antigens provide effective protection of mice against a normally lethal L. Monocytogenes infection after vaccination with attenuated S. typhimurium secreting either LLO or p60. The system developed by Gentschev permits in-frame insertion of a gene or a gene fragments for any given protein antigen and thus includes antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor antigens. (section 3, page 138).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to utilize antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor (which were

well known in the art at the time of filing of the '556 Patent) in place of hlyC, hlyB and hlyD, in the disclosure of Gentschev. The desire to express at least 1 of the recited types of proteins in a target cell, which existed in the art at the time of filing of the '556 Patent, would provide the motivation to do so.

168. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference in view of the Hess reference

Claim 29 of the '556 Patent is dependent on claim 16 and is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and is thus unpatentable.

As shown hereinabove, claim 16 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claim 29 is found in the Gentschev reference. Claim 29 of the '556 Patent recites: "The bacterium of claim 1, wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor".

Claim 29 of the '556 Patent	Gentschev reference
"wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor"	**Gentschev** discloses that the hemolysin secretion machinery can be successfully applied to express and secrete various heterologous antigens. Specifically, Gentschev shows that antibiotic, anti-bacterial, antigens provide effective protection of mice against a normally lethal L. Monocytogenes infection after vaccination with attenuated S. typhimurium secreting either LLO or p60. The system developed by Gentschev permits in-frame insertion of a gene or a gene fragments for any given protein antigen and thus includes antibiotic, insecticide, fungicide, anti-viral

Claim 29 of the '556 Patent	Gentschev reference
	agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor antigens. (section 3, page 138).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to utilize antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor (which were well known in the art at the time of filing of the '556 Patent) in place of hlyC, hlyB and hlyD, in the disclosure of Gentschev. The desire to express at least 1 of the recited types of proteins in a target cell, which existed in the art at the time of filing of the '556 Patent, would provide the motivation to do so.

169. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference in view of US'538 Patent

Claim 29 of the '556 Patent is dependent on claim 16 and is obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent and is thus unpatentable.

As shown hereinabove, claim 16 is obvious under 35 U.S.C.103, over the Gentschev reference in view US'538 Patent.

As shown in the chart below, the element and limitation of claim 29 is found in the Gentschev reference. Claim 29 of the '556 Patent recites: "The bacterium of claim 1, wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor".

Claim 29 of the '556 Patent	Gentschev reference
"wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor"	**Gentschev** discloses that the hemolysin secretion machinery can be successfully applied to express and secrete various heterologous antigens.

Claim 29 of the '556 Patent	Gentschev reference
	Specifically, Gentschev shows that antibiotic, anti-bacterial, antigens provide effective protection of mice against a normally lethal L. Monocytogenes infection after vaccination with attenuated S. typhimurium secreting either LLO or p60. The system developed by Gentschev permits in-frame insertion of a gene or a gene fragments for any given protein antigen and thus includes antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor antigens. (section 3, page 138).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to utilize antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor (which were well known in the art at the time of filing of the '556 Patent) in place of hlyC, hlyB and hlyD, in the disclosure of Gentschev. The desire to express at least 1 of the recited types of proteins in a target cell, which existed in the art at the time of filing of the '556 Patent, would provide the motivation to do so.

170. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference in view of the Hess reference and the Bielecki reference

Claim 29 of the '556 Patent is dependent on claim 16 and is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and the Bielecki reference and is thus unpatentable.

As shown hereinabove, claim 16 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

As shown in the chart below, the element and limitation of claim 29 is found in the Gentschev reference. Claim 29 of the '556 Patent recites: "The bacterium of claim 1, wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor".

Claim 29 of the '556 Patent	Gentschev reference
"wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor"	**Gentschev** discloses that the hemolysin secretion machinery can be successfully applied to express and secrete various heterologous antigens. Specifically, Gentschev shows that antibiotic, anti-bacterial, antigens provide effective protection of mice against a normally lethal L. Monocytogenes infection after vaccination with attenuated S. typhimurium secreting either LLO or p60. The system developed by Gentschev permits in-frame insertion of a gene or a gene fragments for any given protein antigen and thus includes antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor antigens. (section 3, page 138).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to utilize antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor (which were well known in the art at the time of filing of the '556 Patent) in place of hlyC, hlyB and hlyD, in the disclosure of Gentschev. The desire to express at least 1 of the recited types of proteins in a target cell, which existed in the art at the time of filing of the '556 Patent, would provide the motivation to do so.

171. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference in view of the Schmidt reference

Claim 29 of the '556 Patent is dependent on claim 16 and is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference and is thus unpatentable.

As shown hereinabove, claim 16 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claim 29 is found in the Gentschev reference. Claim 29 of the '556 Patent recites: "The bacterium of claim 1, wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor".

Claim 29 of the '556 Patent	Gentschev reference
"wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor"	**Gentschev** discloses that the hemolysin secretion machinery can be successfully applied to express and secrete various heterologous antigens. Specifically, Gentschev shows that antibiotic, anti-bacterial, antigens provide effective protection of mice against a normally lethal L. Monocytogenes infection after vaccination with attenuated S. typhimurium secreting either LLO or p60. The system developed by Gentschev permits in-frame insertion of a gene or a gene fragments for any given protein antigen and thus includes antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor antigens. (section 3, page 138).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to utilize antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor (which were well known in the art at the time of filing of the '556 Patent) in place of hlyC, hlyB and hlyD, in the disclosure of Gentschev. The desire to express at least 1 of the recited types of proteins in a target cell, which existed in the art at the time of filing of the '556 Patent, would provide the motivation to do so.

172. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference and the Hess reference

Claim 29 of the '556 Patent is dependent on claim 16 and is obvious under 35 U.S.C.103, over the Gentschev reference and the Hess reference and is thus unpatentable.

As shown hereinabove, claim 16 is anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claim 29 is found in the in the Hess reference. Claim 29 of the '556 Patent recites: "The bacterium of claim 1, wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor".

Claim 29 of the '556 Patent	Hess reference
"wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor"	**Hess** provides that a bacteria comprising an antibiotic antigen (BCG) is utilized as an antituberculosis vaccine (abstract, page 5299).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to utilize antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor (which were

well known in the art at the time of filing of the '556 Patent) in place of hlyC, hlyB and hlyD, in the disclosure of Hess. The desire to express at least 1 of the recited types of proteins in a target cell, which existed in the art at the time of filing of the '556 Patent, would provide the motivation to do so.

173. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference and the Hess reference

Claim 29 of the '556 Patent is dependent on claim 16 and is obvious under 35 U.S.C.103, over the Gentschev reference and the Hess reference and is thus unpatentable.

As shown hereinabove, claim 16 is obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claim 29 is found in the in the Hess reference. Claim 29 of the '556 Patent recites: "The bacterium of claim 1, wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor".

Claim 29 of the '556 Patent	Hess reference
"wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor"	**Hess** provides that a bacteria comprising an antibiotic antigen (BCG) is utilized as an antituberculosis vaccine (abstract, page 5299).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to utilize antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor (which were well known in the art at the time of filing of the '556 Patent) in place of hlyC, hlyB and hlyD, in the disclosure of Hess. The desire to express at least 1 of the recited types of proteins in a

target cell, which existed in the art at the time of filing of the '556 Patent, would provide the motivation to do so.

174. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference and the Hess reference in view of the Hess reference

Claim 29 of the '556 Patent is dependent on claim 16 and is obvious under 35 U.S.C.103, over the Gentschev reference and the Hess reference in view of the Hess reference and is thus unpatentable.

As shown hereinabove, claim 16 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference.

As shown in the chart below, the element and limitation of claim 29 is found in the in the Hess reference. Claim 29 of the '556 Patent recites: "The bacterium of claim 1, wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor".

Claim 29 of the '556 Patent	Hess reference
"wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor"	**Hess** provides that a bacteria comprising an antibiotic antigen (BCG) is utilized as an antituberculosis vaccine (abstract, page 5299).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to utilize antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor (which were well known in the art at the time of filing of the '556 Patent) in place of hlyC, hlyB and hlyD, in the disclosure of Hess. The desire to express at least 1 of the recited types of proteins in a

target cell, which existed in the art at the time of filing of the '556 Patent, would provide the motivation to do so.

175. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference and the Hess reference in view of US'538 Patent

Claim 29 of the '556 Patent is dependent on claim 16 and is obvious under 35 U.S.C.103, over the Gentschev reference and the Hess reference in view of US'538 Patent and is thus unpatentable.

As shown hereinabove, claim 16 is obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claim 29 is found in the in the Hess reference. Claim 29 of the '556 Patent recites: "The bacterium of claim 1, wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor".

Claim 29 of the '556 Patent	Hess reference
"wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor"	**Hess** provides that a bacteria comprising an antibiotic antigen (BCG) is utilized as an antituberculosis vaccine (abstract, page 5299).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to utilize antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor (which were well known in the art at the time of filing of the '556 Patent) in place of hlyC, hlyB and hlyD, in the disclosure of Hess. The desire to express at least 1 of the recited types of proteins in a

target cell, which existed in the art at the time of filing of the '556 Patent, would provide the motivation to do so.

176. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference and the Hess reference in view of the Hess reference and the Bielecki reference

Claim 29 of the '556 Patent is dependent on claim 16 and is obvious under 35 U.S.C.103, over the Gentschev reference and the Hess reference in view of the Hess reference and the Bielecki reference and is thus unpatentable.

As shown hereinabove, claim 16 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

As shown in the chart below, the element and limitation of claim 29 is found in the in the Hess reference. Claim 29 of the '556 Patent recites: "The bacterium of claim 1, wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor".

Claim 29 of the '556 Patent	Hess reference
"wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor"	**Hess** provides that a bacteria comprising an antibiotic antigen (BCG) is utilized as an antituberculosis vaccine (abstract, page 5299).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to utilize antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor (which were well known in the art at the time of filing of the '556 Patent) in place of hlyC, hlyB and hlyD, in the disclosure of Hess. The desire to express at least 1 of the recited types of proteins in a

target cell, which existed in the art at the time of filing of the '556 Patent, would provide the motivation to do so.

177. A substantial new question of patentability as to claim 29 is raised by the Gentschev reference and the Hess reference in view of the Schmidt reference

Claim 29 of the '556 Patent is dependent on claim 16 and is obvious under 35 U.S.C.103, over the Gentschev reference and the Hess reference in view of the Schmidt reference and is thus unpatentable.

As shown hereinabove, claim 16 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claim 29 is found in the in the Hess reference. Claim 29 of the '556 Patent recites: "The bacterium of claim 1, wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor".

Claim 29 of the '556 Patent	Hess reference
"wherein the agent is selected from an antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor"	**Hess** provides that a bacteria comprising an antibiotic antigen (BCG) is utilized as an antituberculosis vaccine (abstract, page 5299).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to utilize antibiotic, insecticide, fungicide, anti-viral agent, anti-protozoan agent, enzyme, anti-cancer agent, antibody, anti-inflammatory peptide, and transcription factor (which were well known in the art at the time of filing of the '556 Patent) in place of hlyC, hlyB and hlyD, in the disclosure of Hess. The desire to express at least 1 of the recited types of proteins in a

target cell, which existed in the art at the time of filing of the '556 Patent, would provide the motivation to do so.

178. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Dietrich reference

Claim 31 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference, US' 538 Patent, and the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claim 31 is found in the Dietrich reference and in US'538 Patent. Claim 31 of the '556 Patent recites: "The method of claim 16, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell".

Claim 31 of the '556 Patent	Prior Art reference
" [1] the bacterium is endocytosed into a vacuole of the cell, [2] the bacterium undergoes lysis and [3] the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell"	**Dietrich** discloses a bacterium is endocytosed into a macrophage, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell (as evidenced by GFP distribution in the cytosol (page 183). **US'538** Patent discloses an attenuated Shigella as an example of a bacterial delivery system. Shigella invades cells, escape from the phagosome, and enter into the cytoplasm of eukaryotic cells. The attenuated Shigella strain, once inside the host cell, undergoes lysis thus, dieing and releasing its contents (column 2, lines 14-22; column 3, lines 8-13).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to combine the disclosure of US'538 Patent and Dietrich with Gentschev, to obtain a method for introducing a foreign agent into a eukaryotic cell, wherein the bacterium is endocytosed

into a vacuole, the bacterium is lysed, while cytolysin mediates transfer of the agent from the vacuole to the cytosol.

179. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Dietrich reference

Claim 31 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference, US' 538 Patent, and the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claim 31 is found in the Dietrich reference and in US'538 Patent. Claim 31 of the '556 Patent recites: "The method of claim 16, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell".

Claim 31 of the '556 Patent	Prior Art reference
" [1] the bacterium is endocytosed into a vacuole of the cell, [2] the bacterium undergoes lysis and [3] the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell"	**Dietrich** discloses a bacterium is endocytosed into a macrophage, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell (as evidenced by GFP distribution in the cytosol (page 183). **US'538** Patent discloses an attenuated Shigella as an example of a bacterial delivery system. Shigella invades cells, escape from the phagosome, and enter into the cytoplasm of eukaryotic cells. The attenuated Shigella strain, once inside the host cell, undergoes lysis thus, dieing and releasing its contents (column 2, lines 14-22; column 3, lines 8-13).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to combine the disclosure of US'538 Patent and Dietrich with Gentschev, to obtain a method for introducing a foreign agent into a eukaryotic cell, wherein the bacterium is endocytosed

into a vacuole, the bacterium is lysed, while cytolysin mediates transfer of the agent from the vacuole to the cytosol.

180. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Dietrich reference

Claim 31 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 31 is found in the Dietrich reference and in US'538 Patent. Claim 31 of the '556 Patent recites: "The method of claim 16, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell".

Claim 31 of the '556 Patent	Prior Art reference
" [1] the bacterium is endocytosed into a vacuole of the cell, [2] the bacterium undergoes lysis and [3] the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell"	**Dietrich** discloses a bacterium is endocytosed into a macrophage, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell (as evidenced by GFP distribution in the cytosol (page 183). **US'538** Patent discloses an attenuated Shigella as an example of a bacterial delivery system. Shigella invades cells, escape from the phagosome, and enter into the cytoplasm of eukaryotic cells. The attenuated Shigella strain, once inside the host cell, undergoes lysis thus, dieing and releasing its contents (column 2, lines 14-22; column 3, lines 8-13).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to combine the disclosure of US'538 Patent and Dietrich with Gentschev, to obtain a method

for introducing a foreign agent into a eukaryotic cell, wherein the bacterium is endocytosed into a vacuole, the bacterium is lysed, while cytolysin mediates transfer of the agent from the vacuole to the cytosol.

181. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Dietrich reference in view US'538 Patent

Claim 31 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference, US' 538 Patent, and the Dietrich reference in view US'538 Patent and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claim 31 is found in the Dietrich reference and in US'538 Patent. Claim 31 of the '556 Patent recites: "The method of claim 16, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell".

Claim 31 of the '556 Patent	Prior Art reference
" [1] the bacterium is endocytosed into a vacuole of the cell, [2] the bacterium undergoes lysis and [3] the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell"	**Dietrich** discloses a bacterium is endocytosed into a macrophage, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell (as evidenced by GFP distribution in the cytosol (page 183). **US'538** Patent discloses an attenuated Shigella as an example of a bacterial delivery system. Shigella invades cells, escape from the phagosome, and enter into the cytoplasm of eukaryotic cells. The attenuated Shigella strain, once inside the host cell, undergoes lysis thus, dieing and releasing its contents (column 2, lines 14-22; column 3, lines 8-13).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to combine the disclosure of US'538 Patent and Dietrich with Gentschev, to obtain a method for introducing a foreign agent into a eukaryotic cell, wherein the bacterium is endocytosed into a vacuole, the bacterium is lysed, while cytolysin mediates transfer of the agent from the vacuole to the cytosol.

182. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Hess reference and the Bielecki reference

Claim 31 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Hess reference and the Bielecki reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

As shown in the chart below, the element and limitation of claim 31 is found in the Dietrich reference and in US'538 Patent. Claim 31 of the '556 Patent recites: "The method of claim 16, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell".

Claim 31 of the '556 Patent	Prior Art reference
" [1] the bacterium is endocytosed into a vacuole of the cell, [2] the bacterium undergoes lysis and [3] the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell"	**Dietrich** discloses a bacterium is endocytosed into a macrophage, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell (as evidenced by GFP distribution in the cytosol (page 183). **US'538** Patent discloses an attenuated Shigella as an example of a bacterial delivery system. Shigella invades cells, escape from the phagosome, and enter into the cytoplasm of eukaryotic cells. The attenuated Shigella strain, once inside the host cell, undergoes lysis thus,

Claim 31 of the '556 Patent	Prior Art reference
	dieing and releasing its contents (column 2, lines 14-22; column 3, lines 8-13).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to combine the disclosure of US'538 Patent and Dietrich with Gentschev, to obtain a method for introducing a foreign agent into a eukaryotic cell, wherein the bacterium is endocytosed into a vacuole, the bacterium is lysed, while cytolysin mediates transfer of the agent from the vacuole to the cytosol.

183. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Schmidt reference

Claim 31 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Schmidt reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claim 31 is found in the Dietrich reference and in US'538 Patent. Claim 31 of the '556 Patent recites: "The method of claim 16, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell".

Claim 31 of the '556 Patent	Prior Art reference
" [1] the bacterium is endocytosed into a vacuole of the cell, [2] the bacterium undergoes lysis and [3] the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell"	**Dietrich** discloses a bacterium is endocytosed into a macrophage, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell (as evidenced by GFP distribution in the cytosol (page 183). **US'538** Patent discloses an attenuated Shigella as an example of a bacterial delivery system.

Claim 31 of the '556 Patent	Prior Art reference
	Shigella invades cells, escape from the phagosome, and enter into the cytoplasm of eukaryotic cells. The attenuated Shigella strain, once inside the host cell, undergoes lysis thus, dieing and releasing its contents (column 2, lines 14-22; column 3, lines 8-13).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to combine the disclosure of US'538 Patent and Dietrich with Gentschev, to obtain a method for introducing a foreign agent into a eukaryotic cell, wherein the bacterium is endocytosed into a vacuole, the bacterium is lysed, while cytolysin mediates transfer of the agent from the vacuole to the cytosol.

184. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Hess reference

Claim 31 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference, US' 538 Patent, and the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the element and limitation of claim 31 is found in US'538 Patent, and in the Hess reference. Claim 31 of the '556 Patent recites: "The method of claim 16, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell".

Claim 31 of the '556 Patent	Prior Art reference
" [1] the bacterium is endocytosed into a vacuole of the cell, [2] the bacterium undergoes lysis and [3] the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell"	**Hess** discloses that LLO can be used to confer that the bacterium is endocytosed into a vacuole of the cell and that the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell (page 5302). **US'538** Patent discloses an attenuated Shigella

Claim 31 of the '556 Patent	Prior Art reference
	as an example of a bacterial delivery system. Shigella invades cells, escape from the phagosome, and enter into the cytoplasm of eukaryotic cells. The attenuated Shigella strain, once inside the host cell, undergoes lysis thus, dieing and releasing its contents (column 2, lines 14-22; column 3, lines 8-13).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to combine the disclosure of US'538 Patent and Hess with Gentschev, to obtain a method for introducing a foreign agent into a eukaryotic cell, wherein the bacterium is endocytosed into a vacuole, the bacterium is lysed, while cytolysin mediates transfer of the agent from the vacuole to the cytosol.

185. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Hess reference

Claim 31 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference, US' 538 Patent, and the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the element and limitation of claim 31 is found in US'538 Patent, and in the Hess reference. Claim 31 of the '556 Patent recites: "The method of claim 16, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell".

Claim 31 of the '556 Patent	Prior Art reference
" [1] the bacterium is endocytosed into a vacuole of the cell, [2] the bacterium undergoes lysis and [3] the cytolysin mediates transfer of the	**Hess** discloses that LLO can be used to confer that the bacterium is endocytosed into a vacuole of the cell and that the cytolysin mediates transfer of the agent from the vacuole to the

Claim 31 of the '556 Patent	Prior Art reference
agent from the vacuole to the cytosol of the cell"	cytosol of the cell (page 5302). **US'538** Patent discloses an attenuated Shigella as an example of a bacterial delivery system. Shigella invades cells, escape from the phagosome, and enter into the cytoplasm of eukaryotic cells. The attenuated Shigella strain, once inside the host cell, undergoes lysis thus, dieing and releasing its contents (column 2, lines 14-22; column 3, lines 8-13).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to combine the disclosure of US'538 Patent and Hess with Gentschev, to obtain a method for introducing a foreign agent into a eukaryotic cell, wherein the bacterium is endocytosed into a vacuole, the bacterium is lysed, while cytolysin mediates transfer of the agent from the vacuole to the cytosol.

186. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Hess reference in view of the Dietrich reference

Claim 31 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the element and limitation of claim 31 is found in US'538 Patent, and in the Hess reference. Claim 31 of the '556 Patent recites: "The method of claim 16, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell".

Claim 31 of the '556 Patent	Prior Art reference
" [1] the bacterium is endocytosed into a vacuole of the cell, [2] the bacterium undergoes lysis and [3] the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell"	**Hess** discloses that LLO can be used to confer that the bacterium is endocytosed into a vacuole of the cell and that the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell (page 5302). **US'538** Patent discloses an attenuated Shigella as an example of a bacterial delivery system. Shigella invades cells, escape from the phagosome, and enter into the cytoplasm of eukaryotic cells. The attenuated Shigella strain, once inside the host cell, undergoes lysis thus, dieing and releasing its contents (column 2, lines 14-22; column 3, lines 8-13).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to combine the disclosure of US'538 Patent and Hess with Gentschev, to obtain a method for introducing a foreign agent into a eukaryotic cell, wherein the bacterium is endocytosed into a vacuole, the bacterium is lysed, while cytolysin mediates transfer of the agent from the vacuole to the cytosol.

187. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Hess reference in view US'538 Patent

Claim 31 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference, US' 538 Patent, and the Dietrich reference in view US'538 Patent and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of US'538 Patent.

As shown in the chart below, the element and limitation of claim 31 is found in US'538 Patent, and in the Hess reference. Claim 31 of the '556 Patent recites: "The method of claim 16, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium

undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell".

Claim 31 of the '556 Patent	Prior Art reference
" [1] the bacterium is endocytosed into a vacuole of the cell, [2] the bacterium undergoes lysis and [3] the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell"	**Hess** discloses that LLO can be used to confer that the bacterium is endocytosed into a vacuole of the cell and that the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell (page 5302). **US'538** Patent discloses an attenuated Shigella as an example of a bacterial delivery system. Shigella invades cells, escape from the phagosome, and enter into the cytoplasm of eukaryotic cells. The attenuated Shigella strain, once inside the host cell, undergoes lysis thus, dieing and releasing its contents (column 2, lines 14-22; column 3, lines 8-13).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to combine the disclosure of US'538 Patent and Hess with Gentschev, to obtain a method for introducing a foreign agent into a eukaryotic cell, wherein the bacterium is endocytosed into a vacuole, the bacterium is lysed, while cytolysin mediates transfer of the agent from the vacuole to the cytosol.

188. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Hess reference in view of the Hess reference and the Bielecki reference

Claim 31 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Hess reference and the Bielecki reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Hess reference and the Bielecki reference.

As shown in the chart below, the element and limitation of claim 31 is found in US'538 Patent, and in the Hess reference. Claim 31 of the '556 Patent recites: "The method of claim 16, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell".

Claim 31 of the '556 Patent	Prior Art reference
" [1] the bacterium is endocytosed into a vacuole of the cell, [2] the bacterium undergoes lysis and [3] the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell"	**Hess** discloses that LLO can be used to confer that the bacterium is endocytosed into a vacuole of the cell and that the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell (page 5302). **US'538** Patent discloses an attenuated Shigella as an example of a bacterial delivery system. Shigella invades cells, escape from the phagosome, and enter into the cytoplasm of eukaryotic cells. The attenuated Shigella strain, once inside the host cell, undergoes lysis thus, dieing and releasing its contents (column 2, lines 14-22; column 3, lines 8-13).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to combine the disclosure of US'538 Patent and Hess with Gentschev, to obtain a method for introducing a foreign agent into a eukaryotic cell, wherein the bacterium is endocytosed into a vacuole, the bacterium is lysed, while cytolysin mediates transfer of the agent from the vacuole to the cytosol.

189. A substantial new question of patentability as to claim 31 is raised by the Gentschev reference, US' 538 Patent, and the Hess reference in view of the Schmidt reference

Claim 31 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the Gentschev reference, US' 538 Patent, and the Dietrich reference in view of the Schmidt reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the element and limitation of claim 31 is found in US'538 Patent, and in the Hess reference. Claim 31 of the '556 Patent recites: "The method of claim 16, wherein the bacterium is endocytosed into a vacuole of the cell, the bacterium undergoes lysis and the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell".

Claim 31 of the '556 Patent	**Prior Art reference**
" [1] the bacterium is endocytosed into a vacuole of the cell, [2] the bacterium undergoes lysis and [3] the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell"	**Hess** discloses that LLO can be used to confer that the bacterium is endocytosed into a vacuole of the cell and that the cytolysin mediates transfer of the agent from the vacuole to the cytosol of the cell (page 5302). **US'538** Patent discloses an attenuated Shigella as an example of a bacterial delivery system. Shigella invades cells, escape from the phagosome, and enter into the cytoplasm of eukaryotic cells. The attenuated Shigella strain, once inside the host cell, undergoes lysis thus, dieing and releasing its contents (column 2, lines 14-22; column 3, lines 8-13).

It would have been obvious to one skilled in the art at the time of filing the '556 Patent to combine the disclosure of US'538 Patent and Hess with Gentschev, to obtain a method for introducing a foreign agent into a eukaryotic cell, wherein the bacterium is endocytosed into a vacuole, the bacterium is lysed, while cytolysin mediates transfer of the agent from the vacuole to the cytosol.

190. A substantial new question of patentability as to claim 42 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference

Claim 42 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the '556 patent as admitted prior and the Gentschev reference and is thus unpatentable.

As shown hereinabove, claim 30 is anticipated under 35 U.S.C.102 (b), over the Gentschev reference.

As shown in the chart below, the patentees of the '556 Patent admit that the element and limitation of claim 42 was well known in the art at the time of filing of the '556 Patent. Claim 42 of the '556 Patent recites: "The method of claim 30, wherein there is no growth or metabolism of the bacterium in eukaryotic cell".

Claim 42 of the '556 Patent	**The '556 Patent**
"no growth or metabolism of the bacterium in eukaryotic cell "	**The '556** Patent provides that dead bacteria that are non-viable prior to endocytosis by the target cell obviate any microbial growth or metabolism in the target cell (column 4, lines 33-38).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosure of Gentschev with the admitted prior art disclosure of the '556 Patent, to obtain a bacterium exhibiting no growth or metabolism and engineered to deliver a gene encoding a foreign agent, according to the method of Gentschev.

191. A substantial new question of patentability as to claim 42 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference

Claim 42 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the '556 patent as admitted prior and the Gentschev reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference.

As shown in the chart below, the patentees of the '556 Patent admit that the element and limitation of claim 42 was well known in the art at the time of filing of the '556 Patent. Claim 42 of the '556 Patent recites: "The method of claim 30, wherein there is no growth or metabolism of the bacterium in eukaryotic cell".

Claim 42 of the '556 Patent	**The '556 Patent**
"no growth or metabolism of the bacterium in eukaryotic cell "	**The '556** Patent provides that dead bacteria that are non-viable prior to endocytosis by the target cell obviate any microbial growth or metabolism in the target cell (column 4, lines 33-38).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosure of Gentschev with the admitted prior art disclosure of the '556 Patent, to obtain a bacterium exhibiting no growth or metabolism and engineered to deliver a gene encoding a foreign agent, according to the method of Gentschev.

192. A substantial new question of patentability as to claim 42 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Dietrich reference

Claim 42 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the '556 patent as admitted prior and the Gentschev reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the patentees of the '556 Patent admit that the element and limitation of claim 42 was well known in the art at the time of filing of the '556 Patent. Claim 42 of the '556 Patent recites: "The method of claim 30, wherein there is no growth or metabolism of the bacterium in eukaryotic cell".

Claim 42 of the '556 Patent	The '556 Patent
"no growth or metabolism of the bacterium in eukaryotic cell "	**The '556** Patent provides that dead bacteria that are non-viable prior to endocytosis by the target cell obviate any microbial growth or metabolism in the target cell (column 4, lines 33-38).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosure of Gentschev with the admitted prior art disclosure of the '556 Patent, to obtain a bacterium exhibiting no growth or metabolism and engineered to deliver a gene encoding a foreign agent, according to the method of Gentschev and Dietrich.

193. A substantial new question of patentability as to claim 42 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of US'538 Patent

Claim 42 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the '556 patent as admitted prior and the Gentschev reference in view of US'538 Patent and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the patentees of the '556 Patent admit that the element and limitation of claim 42 was well known in the art at the time of filing of the '556 Patent. Claim 42 of the '556 Patent recites: "The method of claim 30, wherein there is no growth or metabolism of the bacterium in eukaryotic cell".

Claim 42 of the '556 Patent	The '556 Patent
"no growth or metabolism of the bacterium in eukaryotic cell "	**The '556** Patent provides that dead bacteria that are non-viable prior to endocytosis by the target cell obviate any microbial growth or metabolism in the target cell (column 4, lines 33-38).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosure of Gentschev with the admitted prior art disclosure of the '556 Patent, to obtain a bacterium exhibiting no growth or metabolism and engineered to deliver a gene encoding a foreign agent, according to the method of Gentschev and US'538 Patent.

194. A substantial new question of patentability as to claim 42 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Bielecki reference and the Hess reference

Claim 42 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the '556 patent as admitted prior and the Gentschev reference in view of the Dietrich reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Dietrich reference.

As shown in the chart below, the patentees of the '556 Patent admit that the element and limitation of claim 42 was well known in the art at the time of filing of the '556 Patent. Claim 42 of the '556 Patent recites: "The method of claim 30, wherein there is no growth or metabolism of the bacterium in eukaryotic cell".

Claim 42 of the '556 Patent	**The '556 Patent**
"no growth or metabolism of the bacterium in eukaryotic cell "	**The '556** Patent provides that dead bacteria that are non-viable prior to endocytosis by the target cell obviate any microbial growth or metabolism in the target cell (column 4, lines 33-38).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosure of Gentschev with the admitted prior art disclosure of the '556 Patent, to obtain a bacterium exhibiting no growth or metabolism and engineered to deliver a gene encoding a foreign agent, according to the method of Gentschev, Hess and Bielecki.

195. A substantial new question of patentability as to claim 42 is raised by the '556 Patent over self admitted Prior Art and the Gentschev reference in view of the Schmidt reference

Claim 42 of the '556 Patent is dependent on claim 30 and is obvious under 35 U.S.C.103, over the '556 patent as admitted prior and the Gentschev reference in view of the Schmidt reference and is thus unpatentable.

As shown hereinabove, claim 30 is obvious under 35 U.S.C.103, over the Gentschev reference in view of the Schmidt reference.

As shown in the chart below, the patentees of the '556 Patent admit that the element and limitation of claim 42 was well known in the art at the time of filing of the '556 Patent. Claim 42 of the '556 Patent recites: "The method of claim 30, wherein there is no growth or metabolism of the bacterium in eukaryotic cell".

Claim 42 of the '556 Patent	**The '556 Patent**
"no growth or metabolism of the bacterium in eukaryotic cell "	**The '556** Patent provides that dead bacteria that are non-viable prior to endocytosis by the target cell obviate any microbial growth or metabolism in the target cell (column 4, lines 33-38).

It would have been obvious to a person skilled in the art at the time of the filing of the '556 Patent to combine the disclosure of Gentschev with the admitted prior art disclosure of the '556 Patent, to obtain a bacterium exhibiting no growth or metabolism and engineered to deliver a gene encoding a foreign agent, according to the method of Gentschev and Schmidt.

V. CONCLUSION

Based on Gentschev, US'538 Patent, Bielecki, Hess, Dietrich, and/or admitted prior art in the specification of the '556 Patent, claims 1-42 of the '556 Patent are not patentable. Specifically, the subject matter of claims 1, 16, and 30 are anticipated and/or obvious in view of Gentschev, either alone and/or in combination with US'538 Patent, Bielecki, Hess, Dietrich and/or admitted prior art in the specification of the '556 Patent. Claims 2-15, 17-29, and 31-42 of the '556 Patent depend from claims 1, 16, and 30, respectively, thus containing all their limitations by reference, and reciting the additional limitations set forth hereinabove. The additional limitations recited in claims 2-15, 17-29, and 31-42 are anticipated and/or obvious in view of Gentschev, either alone and/or in combination with US'538 Patent, Bielecki, Hess, Dietrich, and/or admitted prior art in the specification of the '556 Patent.

Since all the claim limitations of claim 1, 16, and 30 and the additional claim limitations of claims 2-15, 17-29, and 31-42 are anticipated and/or obvious in view of the above prior art references, all the claims are not patentable and reexamination certificate to that effect should be issued forthwith.

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